STUDIES ON HETEROCYCLES OF MEDICINAL INTEREST

A THESIS

SUBMITTED TO THE

SAURASHTRA UNIVERSITY

FOR THE DEGREE OF

Doctor of Philosophy

IN

THE FACULTY OF SCIENCE (CHEMISTRY)

BY

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UNDER THE GUIDANCE

OF

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Statement under O. Ph. D. 7 of Saurashtra University

The work included in the thesis is my own work under the supervision of ***Dr. H. S. Joshi*** and leads to some contribution in chemistry subsidised by a number of references.

Dt. : -06-2005
Place : Rajkot.

(Paresh D. Zalavadiya)

This is to certify that the present work submitted for the Ph.D. Degree of Saurashtra University by ***Paresh D. Zalavadiya*** is his own work and leads to advancement in the knowledge of chemistry. The thesis has been prepared under my supervision.

Date : -06-2005
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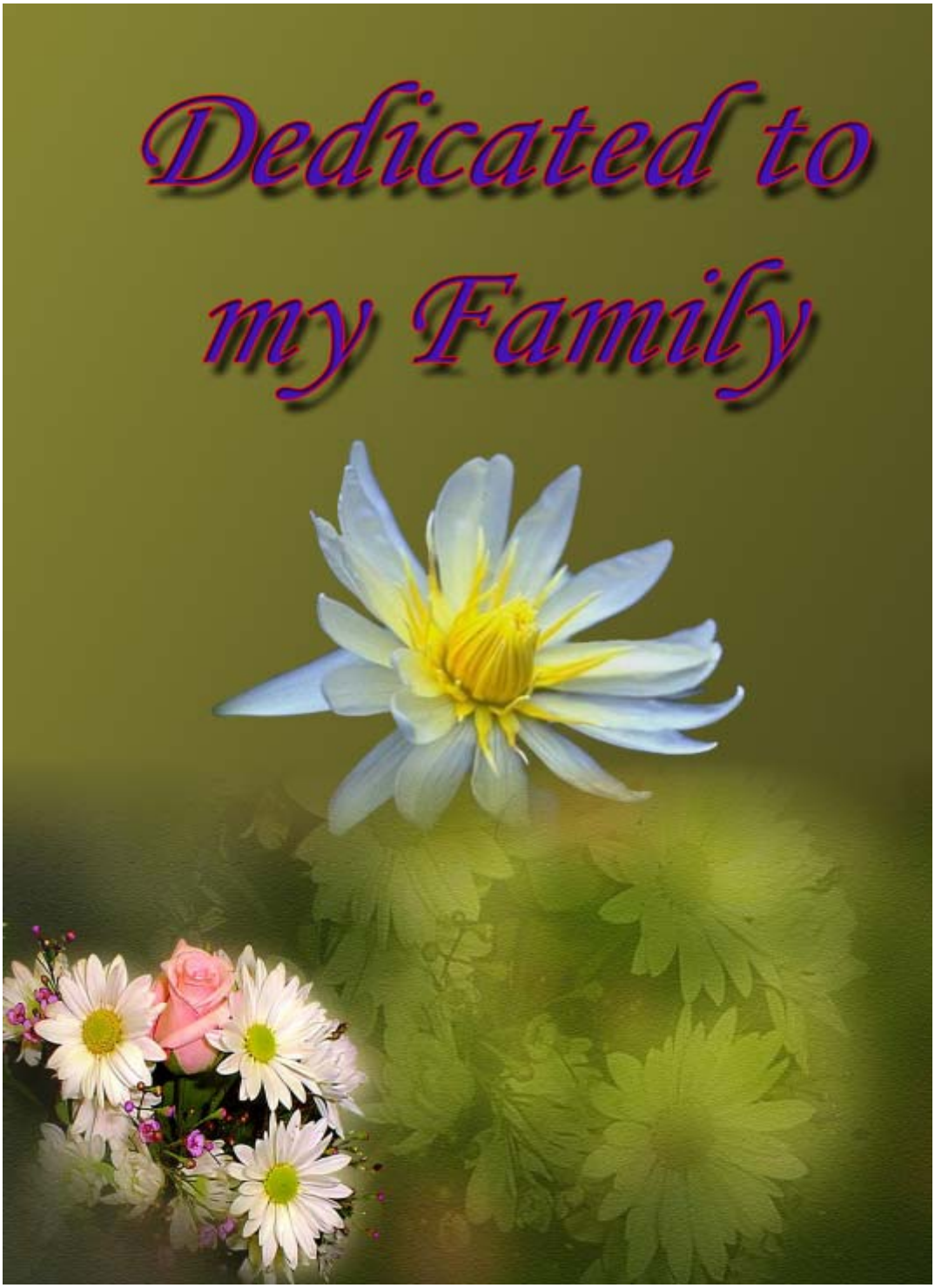
Dedicated to
my Family

Acknowledgement

It is a matter of immense pleasure and proud priviledge for me to express my heartfull gratitude to all those personality who have been helping me in diversified ways. First and foremost I pay all my homage and devote my emotions to "Saraswati Mata" without whose blessing this task would not have been accomplished.

It with great pleasure and with a deep sense of gratitude to my esteemed guide Dr. H. S. Joshi Associate Professor, Department of Chemistry, Saurashtra University, Rajkot for his sagacious and ever vigilunt guidance throughout the course of my Ph. D. work. The only way to thanks him would be perhaps to strive to work similarly in years ahead and continue the chain succession.

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my path and boosting me to go ahead to reach the goal. However I assure them to be worthy of whatever they have done for me.

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I offer my heartfelt gratitude to my intimate friends Dushyant, Dinesh, Praful, Manvar, Jignesh, Aki, Pankaj, Mahesh, Mayur, Sunil, Vishal, Rupesh, Jayesh, Mishra, Vrajlal , Prakash, and all my senior and juniors for their support and constructive criticism at various stages.

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I am thankful to Mr. Harshad Joshi and Mrs. Namrata for their kind support and providing chemicals and glasswares on time.

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Paresh D. Zalavadiya

CONTENTS

STUDIES ON HETEROCYCLES OF MEDICINAL INTEREST

SYNOPSIS

"STUDIES ON HETEROCYCLES OF MEDICINAL INTEREST"

The work incorporated in the thesis with the title **STUDIES ON HETEROCYCLES OF MEDICINAL INTEREST** included investigations pertaining to dihydropyrimidine and their derivatives have been described as under.

PART - I : STUDIES ON DIHYDROPYRIMIDINONES

PART - II : STUDIES ON DIHYDROPYRIMIDINTHIONES

PART - I : STUDIES ON DIHYDROPYRIMIDINONES

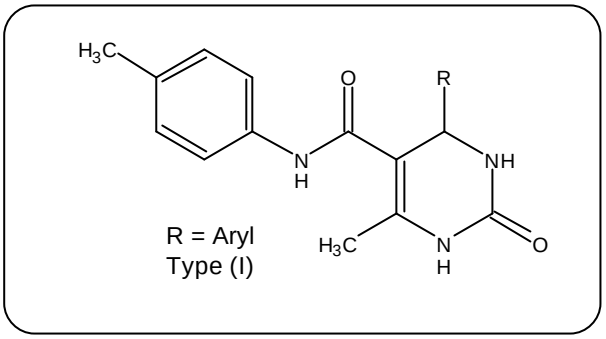
Dihydropyrimidinone and their derivatives represent one of the most active class of compounds possessing a wide spectrum of bilogogical activities such as antiinflammatory, antiviral, antibacterial, antitumor, calcium channel blokers,antihypertenvsive agent and anticancer drugs. Many of their derivatives are pharmacologically important as α_{1a} adrenoceptor selective antagonists. In bening prostatic hyperplasia(BPH) which is a urological disorder in the aging male population.

Several recently isolated marine alkaloids with interesting biological activities also contain the dihydropyrimidinone nucleous.Most notably among these are the batzelladines alkaloids. They inhibit the binding of HIV gp-120 to CD_4 cells and therefore are potential leads for AIDS therapy.

Recently the dihydropyrimidinones have been imolicated in the catabolism of pyrimidine base.Their nucleosides and nucleotides play an important role as antivirus and anticancer agents and they act as a fungicide to inhibit ergosterol biosynthesis by inhibiting the P-450 enzyme.

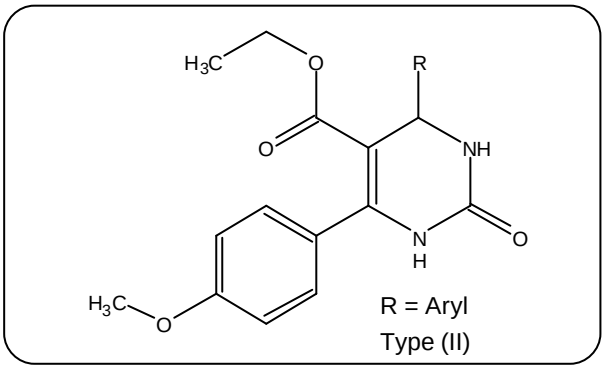
In order to develope better medicinally important compounds, it was considered of interest to synthesize some new dihydropyrimidinone derivatives shown as under.

SECTION-I : Synthesis and biological screening of 6-Methyl-N-(4-methyl phenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxamides.



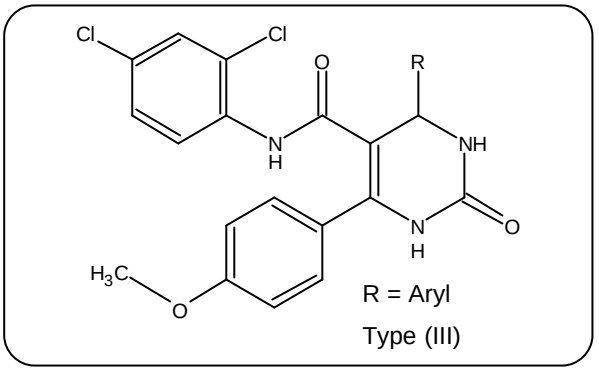
Dihydropyrimidinones of Type (I) have been synthesized by the condensation of N-(4-methylphenyl)-3-oxobutanamide,urea and aryl aldehydes.

SECTION-II : Synthesis and biological screening of Ethyl-6-(4-methoxy phenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxylates.



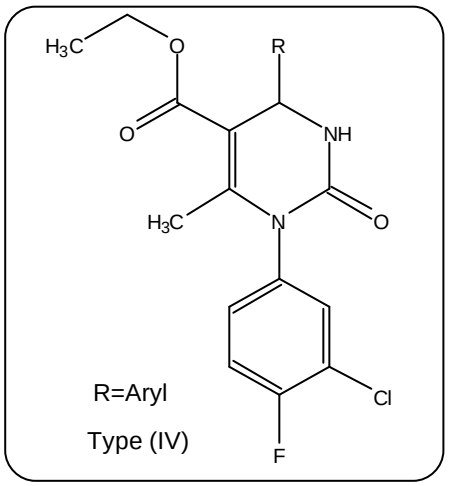
The 6-(4-methoxyphenyl) dihydropyrimidinone carboxylates of Type (II) have been synthesized by the condensation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate,urea and aryl aldehydes.

SECTION-III : Synthesis and biological screening of N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxamides.



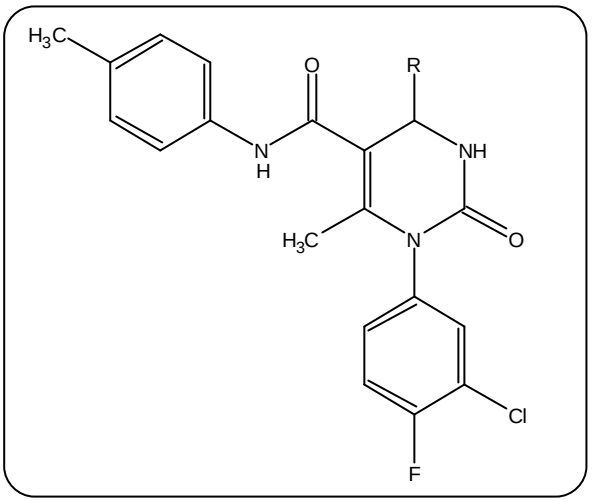
The N-(2,4-dichlorophenyl)-6-(4-methoxyphenyl)dihydropyhimidinone carboxamides of Type (III) have been synthesized by the condensation of N-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide,urea and aryl aldehydes.

SECTION-IV : Synthesis and biological screening of Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one -5-carboxylates.



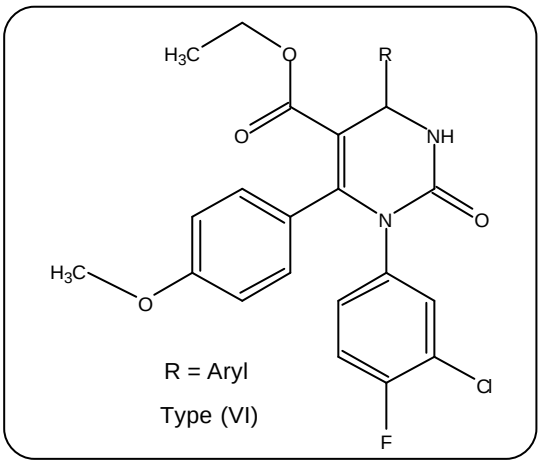
The N-substituted dihydropyrimidinone carboxylates of Type (IV) have been prepared by the condensation of ethylacetoacetate,N-(3-chloro-4-fluorophenyl) urea and aryl aldehydes.

SECTION-V : Synthesis and biological screening of 1-(3-Chloro-4-fluoro phenyl)-4-aryl-6-methyl-N-(4-methylphenyl)-3,4-dihydro pyrimidin-2-one-5-carboxamides.



The N-substituted dihydropyrimidinone carboxymides of Type (V) have been synthesized by the condensation of N-(4-methylphenyl)-3-oxobutanamide,N-(3-chloro-4-fluorophenyl)urea and aryl aldehydes.

SECTION-VI : Synthesis and biological screening of Ethyl-1-(3-chloro-4-fluoro phenyl)-4-aryl-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2-one-5-carboxylates.



N-Substituted dihydropyrimidinone carboxylates of Type (VI) have been synthesized by the condensation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate, N-(3-chloro-4-fluorophenyl)urea and aryl aldehydes.

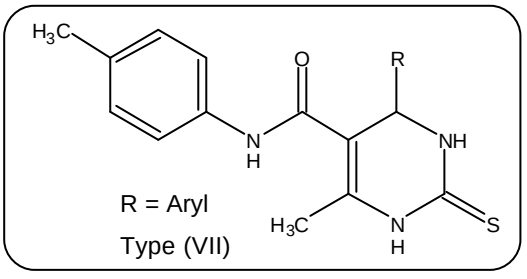
PART - II : STUDIES ON DIHYDROPYRIMIDINTHIONES

The ring system having a thio group occupy a unique position in medicinal chemistry. This type of derivatives play an important role in biological processess and in synthetic drugs. Dihydropyrimidinthione also occur very widely in nature. It is one of the component of nucleic acid, several analogs have been used as compounds that interfere with the synthesis and functioning of nucleic acids, an example is thiouracil which has been used in cancer treatment.

Dihydropyrimidinthione and its derivatives have been center of interest for reaction for research chemist as they possess varied therapeutic activities such as significant in vitro activity against unrelated DNA and RNA virues, antimalarial, diuratic, antimicrobial, antilukemic and antineoplastic.

Keeping the association of dihydropyrimidinonthione derivatives with varid biological activity, it was thought worthwhile to synthesize some new dihydropyrimidinonthione derivatives as under.

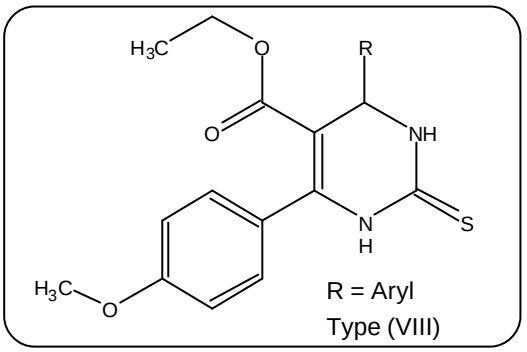
SECTION-I : Synthesis and biological screening of 6-Methyl-N-(4-methyl phenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxamides.



Type (VII)

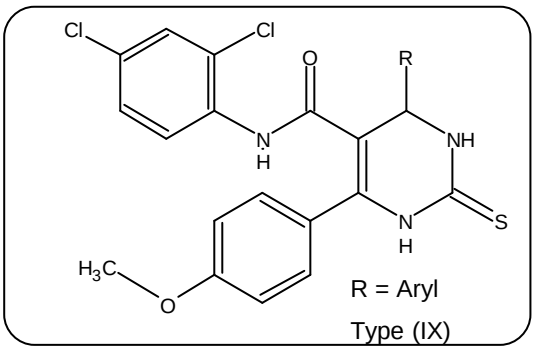
The synthesis of dihydropyrimidinthiones of Type (VII) have been undertaken by the cyclocondensation of N-(4-methylphenyl)-3-oxobutanamide, thiourea and aryl aldehydes.

SECTION-II : Synthesis and biological screening of Ethyl-6-(4-methoxy phenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxylates.



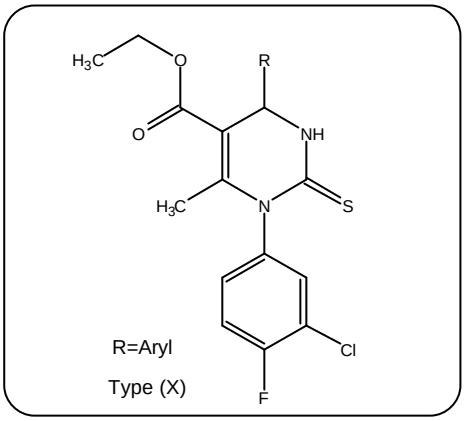
The 6-(4-methoxyphenyl) dihydropyrimidinthione carboxylates of Type (VIII) have been synthesized by the condensation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate,thiourea and aryl aldehydes.

SECTION-III : Synthesis and biological screening of N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl)-4-aryl- 3,4-dihydropyrimidin-2(1H)-thione- 5-carboxamides.



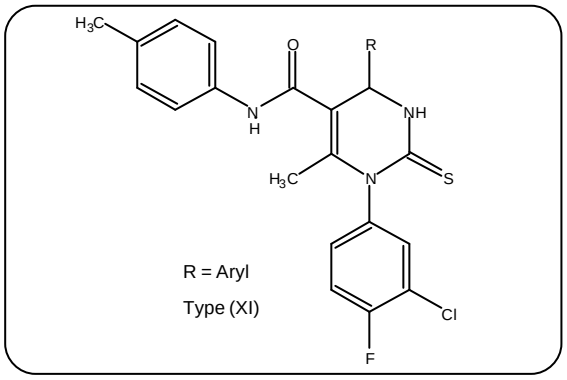
N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl) dihydropyhimidinthione carboxamides of Type (IX) have been synthesized by the condensation of N-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide,thiourea and arylaldehydes.

SECTION-IV : Synthesis and biological screening of Ethyl-1-(3-chloro-4-fluoro phenyl)-4-aryl-6-methyl- 3,4-dihydropyrimidin-2-thione-5-carboxylates.



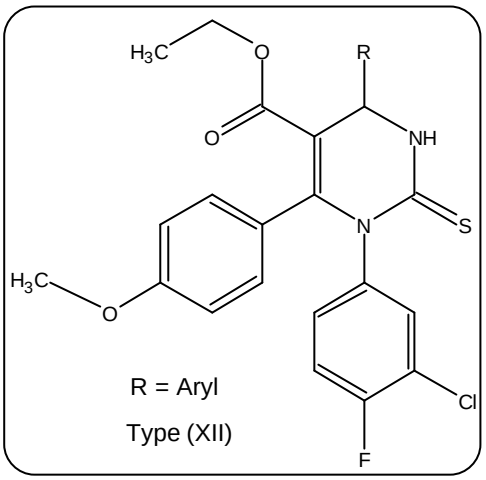
The N-substituted dihydropyrimidinthione carboxylates of Type (X) have been synthesized by the condensation of ethylacetoacetate, N-(3-chloro-4-fluorophenyl) thiourea and aryl aldehydes.

SECTION-V : Synthesis and biological screening of 1-(3-Chloro-4-fluoro phenyl)-4-aryl-6-methyl-N-(4-methylphenyl)-3,4-dihydro pyrimidin-2-thione-5-carboxamides.



The N-substituted dihydropyrimidinthione carboxymides of Type (XI) have been synthesized by the condensation of N-(4-methylphenyl)-3-oxobutanamide,N-(3-chloro-4-fluorophenyl)thiourea and aryl aldehydes.

SECTION-VI : Synthesis and biological screening of Ethyl-1-(3-chloro-4-fluoro phenyl)-4-aryl-6-(methoxyphenyl)-3,4-dihydropyrimidin-2-thione-5-carboxylates.



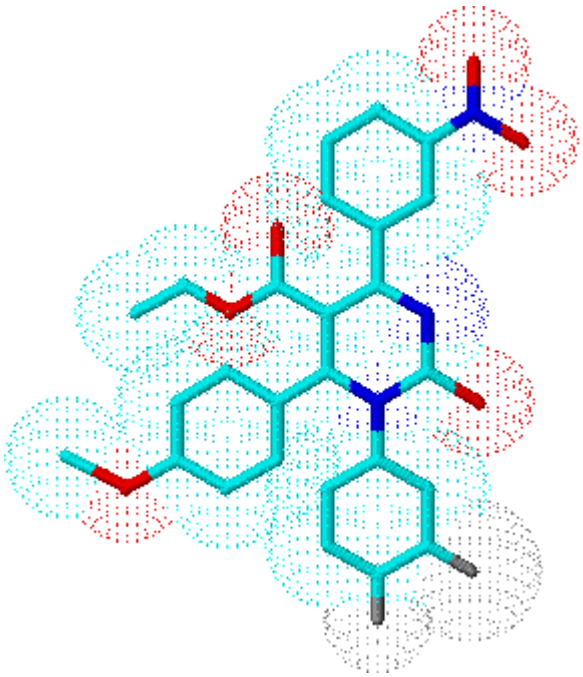
The N-substituted dihydropyrimidinthione carboxylates of Type (XII) have been synthesized by the condensation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate,N-(3-chloro-4-fluorophenyl)thiourea and aryl aldehydes.

The constitution of all above products has been supported by elemental analyses and spectral studies like IR, 1H NMR and Mass spectroscopy. The purity of the compounds synthesized was checked by TLC.

***In vitro* study on multiple biological activities:**

[1] Selected compounds have been evaluated for their ***in vitro*** biological assay like antitubercular activity towards a strain of ***Mycobacterium tuberculosis H37Rv*** at a concentration of 6.25 µg/ml using Rifampin as a standard drug, which have been tested by Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF), Alabama U.S.A.

[2] All the compounds have been evaluated for their antibacterial activity towards Gram positive and Gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration 40 µg/ml. The biological activities of the synthesized compounds have been compared with standard drugs.



PART - I

STUDIES ON

DIHYDROPYRIMIDINONES

GENERAL INTRODUCTION

The chemistry of the heterocyclic compounds is as logical as that of aliphatic or aromatic compounds. This study is of great interest both from the theoretical as well as practical stand point. A heterocyclic compound is one which possesses acyclic structure with at least two different kinds of atoms in the ring. The most common type, contain largely carbon atom, nitrogen, oxygen and sulphur are the most common heteroatoms, but many other elements, including even bromine, chlorine can also serve. The heterocyclic compounds containing the less common atoms have been subject to much investigation in recent years.

The variety of heterocyclic compounds is enormous, their chemistry is complex and synthesizing them requires great skill. Among large number of heterocycles found in nature nitrogen heterocycles are most abundant than those containing oxygen of sulphur owing to their wide distribution in nucleic acid instance and involvement in almost every physiological process of plants and animals.

Heterocyclic systems are encountered in many groups of organic compounds possessing great applicability in industry as well as in our life in various ways i. e. most of the sugars and their derivatives, including vitamin C, for instance, exist largely in the form of five membered (Furanosied str.) or six membered (Pyranoised str.) ring containing one oxygen atom. Most members of the vitamin B group possess heterocyclic rings containing nitrogen, one examples is vitamin B6 (Pyridoxine), which is a derivative of the pyridine essential in amino acid metabolism. Many other examples of the importance of heterocyclic compounds in biological systems can be given.

Natural products containing heterocyclic compounds such as alkaloids and glycosides have been used since old age, as remedial agents. Febrifagl alkaloid from ancient Chinese drug, Chang Shan, reserpine from Indian rouwopifia, Curen alkaloid from arrow poison, codenine, φ-tropine and strychnine are all examples of heterocyclic compounds. Many antibiotics including penicillin, cephalosporin, norfloxacin,

streptomycin etc. also contain heterocyclic ring systems. Majority of the large number of drugs being introduced in pharmacopeias in recent years are heterocyclic compounds.

Many veterinary products like pyrantel and morantel are the drug of choice as broad spectrum anthelmintics. The herbicides atrazine and simazine are well known example of heterocyclic agrochemicals. Plant pigments such as indigo, hemoglobin and anthiocyanins, chlorophyll has contributed much colour chemistry and many other heterocyclic colouring matters are in use since prehistoric times. The heterocyclic tetraselena fulvalene was the first ionic molecular crystal to demonstrate superconductivity.

Heterocyclic compounds are obtainable by the following methods.

(a) Isolation from natural sources, i.e. alkaloids, amino acids, indigo dyes etc.

(b) Degradation of natural products i.e. acridine, furfural, indol, pyridine, quinoline, thiophene etc.

(c) Synthesis: Synthesis methods for obtaining heterocyclic compounds may be divided into ring closer reactions, addition reaction and replacement reaction. Cyclisation is usually accomplished by elimination of some small molecules such as water or ammonia from chain of suitable length.

Heterocyclic compounds have a great applicability as drugs because,

(i) They have a specific chemical reactivity.

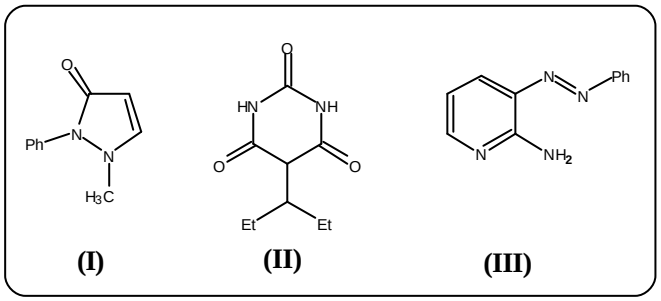
(ii) They resemble essential metabolism and can provide false synthons in biosynthetic process.

The current interest in the creation of large, searchable libraries of organic compounds has captured an imagination of organic chemists and the drug discovery community. Efforts in numerous laboratories focused on the introduction of chemical diversity have been recently reviewed and pharmacologically interesting compounds have been identified for libraries of widely different compositions.

Research in the field of pharmaceutical has its most important task in the development of new and better drugs and their successful introduction into clinical practice. Central to these efforts, accordingly stand the search for pharmaceutical substances and preparation which are new and original. In addition to these objectives the searching for drug which exhibit a clear advantage over a drug already known. Such advantages may be qualitative or quantitative improvement in activity, the absence of undesirable side effect, a lower toxicity, improved stability of decreased cost.

It is important at the outset to note that drug discovery is not an unambiguous term in the pharmaceutical R & D world. For example, it can be defined using either programmatic or organizational approaches (or both), with several options on each category. Hence, it is important first to understand this variability and to adopt a specific definition for the purpose of this discussion.

The contribution of organic chemistry to be development of scientific medicine in the 19th century mainly from acyclic and carbocyclic compounds, although the pyrazoline antipyrin **(I)** was introduced as an antipyretic and analgesic in 1984 and the first barbiturate baritone (veranol) **(II)** in 1903. Guttmann treated, malaria with methylene blue in 1891, with slight success, and in 1912 he introduced acriflavine as trypancide, it has proved to be more valuable as an antiseptic. Phenazopyridini (pyridium)**(III)** was introduced for the same purpose in 1926, and although it is relatively ineffective it has continued to be used since it has some analgesic action.



(I) **(II)** **(III)**

AIMS AND OBJECTIVES

In the pharmaceutical field, these has always been and will continue to be a need for new and novel chemical inhibition of biological fraction. Our efforts are focused on the introduction of chemical diversity in the molecular framework in order to synthesizing pharmacologically interesting compounds of widely different composition.

During the course of our research work, looking to the application of heterocyclic compounds, several entities have been designed, generated and characterized using spectral studies. The details are as under.

1. To generate several biologically active moieties such as dihydropyrimidinones, dihydropyrimidinthiones,dihydropyrimidinone C-5 amides, dihydro pyrimidin thione C-5 amides and N-1 substituted derivatives
2. To characterise these products for structure elucidation using various spectroscopic techniques like IR, PMR and mass spectral analysis.
4. To evaluate these new products for better drug potential against different strains of bacteria, fungi and antitubercular activity by Tuberculosis and Antitumor Acquisation Coordinating Facility (TAACF) Southern Research Institute, Alabama, U.S.A.
5. Purity of all compounds have been checked by thin layer chromatography.

In view of these facts, the research work presented in the theis are described in following parts.

PART-I : STUDIES ON DIHYDROPYRIMIDINONES.

PART-II : STUDIES ON DIHYDROPYRIMIDINTHIONES.

INTRODUCTION

Pyrimidine is the most important member of all the diazines as this ring system occurs widely in living organisms. Purines, uric acid, barbituric acid and anti-malarial and anti-bacterial agents also contain the pyrimidine ring. The chemistry of pyrimidine has been widely studied. Pyrimidine was first isolated by Gabriel and Colman in 1899. Since pyrimidine is symmetrical about the line passing C-2 and C-5, the positions C-4 and C-6 are equivalent and so are N-1 and N-3. When a hydroxyl or amino group is present at the 2-, 4-, of 6-, position than they are tautomeric with oxo and imino respectively.

Despite the importance of dihydroazines (particularly those containing the 1,4-dihydropyrimidine and dihydropyridine moiety[1]) for clarifying a wide range of theoretical, medicinal and biological problems, the chemistry of this group of compounds is still extremely spotty.[2-6] A deeper knowledge of the behavior of this class of compounds is, therefore, desirable. From the theoretical view point, it is essential to predict the structure, binding properties, chemical reactivity, etc. of dihydro compounds from the number and positioning of nitrogen atoms in the ring, as well as from the disposition of double bonds. Such quantum mechanical calculations also enable an evaluation of the degree of aromatic character in potential “homoaromatic” and “antiaromatic” isomers. Availability of novel model compounds for verifying these predictions would open up new horizons in theoretical heterocyclic chemistry, particularly in clarifying the structures leading to spontaneous isomerization of a derivative or in verifying its redox properties.

From the biochemical point of view, dihydroazines are of intense interest because of presence of this group at the active site of the “hydrogen transferring coenzyme” NADH (reduced nicotinamide adenine dinucleotide). This nucleotide, a central participant in metabolic processes in living organisms, participates in the reduction of various unsaturated functionalities.

In the area of drug development, dihydroazines show great promise, particularly since the 4-aryldihydropyridines exhibit powerful vasodilation activity via modifying the calcium ion membrane channel.[7-11] Additionally, dihydropyridines have been found to actively transport medication across biological membranes.[12]

Until recently, most of the information available on dihydroazines centered around dihydropyridines, with very little data extending to the related dihydropyrimidines.

This lacuna has motivated our deep involvement in developing dihydropyrimidine chemistry, particularly dihydropyrimidines containing no substituents on the ring nitrogen.[13] These molecules have long been considered unstable for oxidation, polymerization or disproportionation reactions.[14]

Figure **(1)** depicts the five possible isomeric structures of dihydropyrimidines, exhibiting different dispositions of the double bonds.

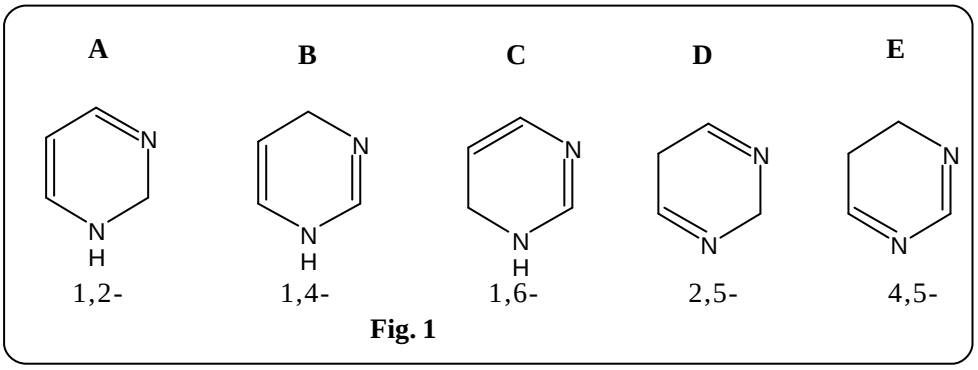


Fig. 1

However, these structures are not easy to synthesize and, as a result, most of the known dihydropyrimidines have either 1,2- (A) or the tautomeric 1,4- (B) and 1,6- **(C)** geometry. On the basis of data available in the literature,[15,16] the dihydropyrimidines can be conveniently divided into two groups, within each of which interconversion between isomers is possible under thermal conditions, namely, the 1,4- (B), 1,6- **(C),** and 4,5- (E) compounds, and the **1,2-** (A) and 2,5- (D) isomers. It is worthwhile to note that, while thermal interconversion between the two groups is not observed, photochemical rearrangement of 1,4-(or 1,6-)dihydropyrimidines to 1,2-isomers has been reported.[17,18]

It should be stressed that dihydroazines take part in various isomerization processes, usually characterized by reversible or irreversible migrations within the ring, the study of which is still in its infancy. Hydrogen migration, for example, is classified either as rearrangement or tautomerism depending on its kinetic and thermodynamic parameters; the former term is reserved for irreversible processes, while the latter is used to describe fast reversible exchanges.[19] A study of isomerization in dihydropyrimidines provides an excellent opportunity for clarifying the factors regulating these processes.

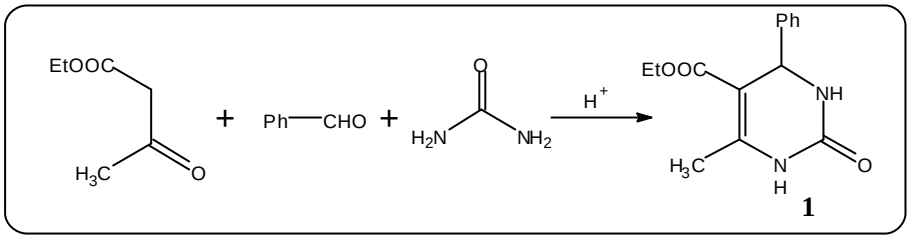
After successfully developing versatile synthetic techniques for obtaining a variety of 1,4- and 1,6-dihydropyrimidines,[20-22] as well as the observation of amidinic tautomerism between the two,[23,24] A. L. Weis et al.[15] examining the possibility of preparative synthesis of similarly N-unsubstituted 1,2-dihydro derivatives and studying their properties. Particularly important goals of this study were the possible observation of the formally allowed hydrogen shift,[23] of "homoaromaticity",[25,26] or of imine-enamine tautomerism[27] in these compounds, behaviors of which have been seen in other systems.

To date few reports on the formation of 1,2-dihydropyrimidines exist in the literature, and in those cases where a product could be isolated and characterized, the material was either an N-substituted derivative or else it contained geminal disubstitution at position **2**, situations that prevent the molecule from oxidizing to the corresponding pyrimidine.

Pyrimidine ring carrying various subtituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other synthesis, which are complimentary rather than alternative to it. A second type of synthesis is the isomerisation or break down of another heterocycles such as an hydration of purine but such roots are frequently used.

SYNTHETIC ASPECT :-

(1) In 1893 Pietro Biginelli reported the first synthesis of dihydropyrimidines of type-**(1)** by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde and urea under strongly acidic condition.[28,29]



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(2) Silica sulfuric acid efficiently catalyzes the three component Biginelli reaction between an aldehyde, a β-cabonyl compound and urea in ethanol to afford the corresponding DHPMs in high yield.[30] The catalyst is reusable and can be applied several times without any decrease in the yield of the reaction.

(3) A novel one-pot condensation of an aldehyde, β-keto-ester and urea was performed using iodotrimethylsilane in acetonitrile for the first time at room temperature affording DHPMs.[31]

(4) Some Biginelli compounds were synthesized by using a photochemistry method. The Biginelli three component cyclocondensation reaction in THF medium using a mixture of β-ketoester or β-diketone, aryl aldehyde and urea under irradiation with a tungstan lamp light gave DHPM-2-(1H)-ones.[32]

(5) Substituted 3,4-DHPM-2(1H)-ones were prepared in high yield by Biginelli condensation of an aldehyde, a dicarbonyl compound and urea in ethanol using $CoCl_2.6H_2O$ catalyst.[33]

(6) DHPM-2(1H)-ones derivatives were effectively synthesized on the solution polyethylene glycol (PEG) 4000,[34] by heating or solvent-free Microwave iradiation through the Biginelli three component cyclo condensation.

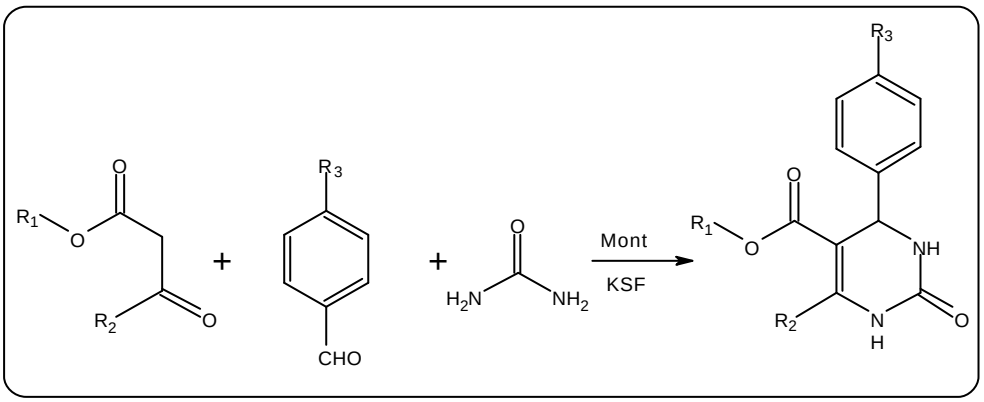
(7) DHPM-2-(1H)-one was prepared from three component β-diketone, aldehyde and urea coupling in ethanol catalyze by indium(III) tribromide($InBr_3$).[35,36] This modified one-pot Biginelli condensation provided not only simple preparation but also this modified Biginelli reaction was oxygen-bridge.

(8) A series of Biginelli compounds was synthesized using 4-methyl benzenesulfonic acid as a catalyst under, microwave irradiation.[37] This simple method provided dihydropyrimidin-2-one in 86-98% yield.

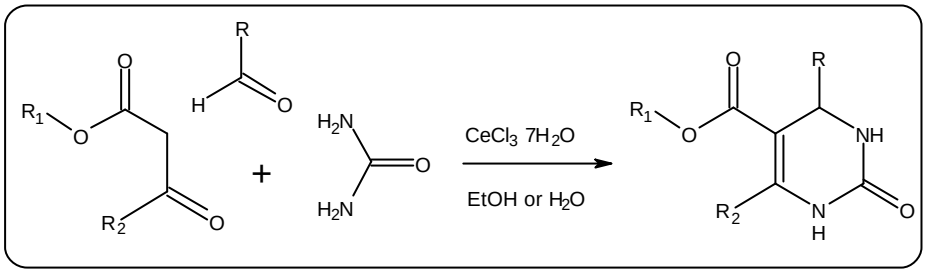
(9) A simple effective synthesis of DHPM-2-(1H)-one derivatives, using boric acid as a catalyst from an aldehyde 1,3-dicarbonyl compound and urea in glacial acetic acid is discribed.[38] Compared with the classical Biginelli reaction conditions, this new method has the advantage of excellent yield 86-97% and the short reaction time (0.5-2hr).

(10) Montmorillonite clays have been widely used in organic synthesis due to their ready availability, easy to set up and work up, mild experimental condition and high yield and selectively. Recently, Bigi[39] reported that the Biginelli reaction could be performed under solvent less conditions using KSF montmorillonite.

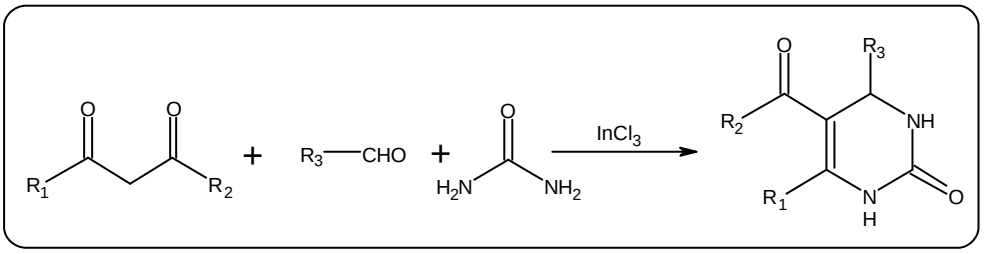
While optimizing the reaction conditions of the Biginelli reaction Haixisa Lin.[40] found that treatment of β-ketoester, aryl aldehyde and urea with KSF montmorillonite in methanol affords DHPMs in good to excellent yield.



(11) Subhas D. Bose et al.[41] describe a general and practical route for the Biginelli cyclocondensation reaction using cerium(III) chloride ($CeCl_3$) heptahydrate as catalyst. Three different sets of reaction conditions were examined (I) traditional ethanol reflux (ii) water reflux and (iii) solvent-free conditions. This is a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields of the DHPM-2(1H)-ones.

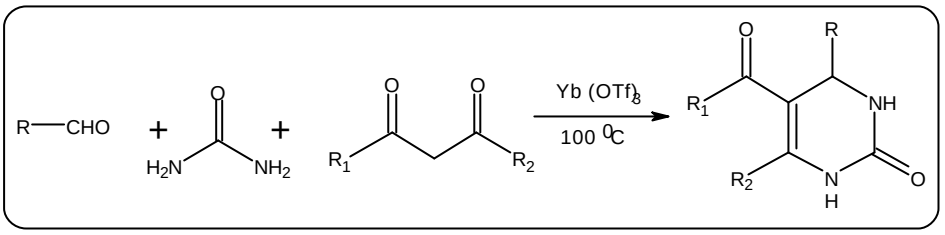


(12) Recently, Indium(III) chloride was emerged as a powerful Lewis catalyst imparting high region and chemo selectivity in various chemical transformations. Ranu C.et al.[42] describe a simple synthesis of DHPM-2-(1H)-one derivatives, using indium(III) chloride (10 mol %) as a catalyst from an aldehyde, β-dicarbonbyl compound and urea in THF.



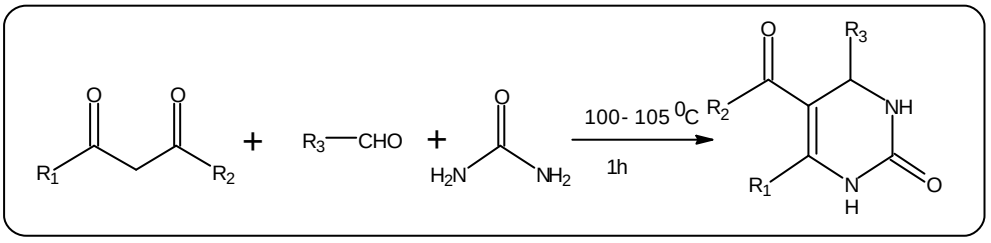
(13) Novel one-pot Biginelli-type reaction was developed by Cnangtao Q. et al.[43] An aromatic or aliphatic aldehydes with β-dicarbonyl compounds and urea heated in the presence of catalytic amount of (5 mol %)$Yb(OTf)_3$ for 60-90 min. under solvent free condition afford the corresponding DHPM-2-(1H) ones.The yield of classical Biginelli reaction can be increased from 20-50%

to 81-91% with reaction time shorted from 18-48 hr. to 60-90 min. The catalyst can be easily recovered and reused.



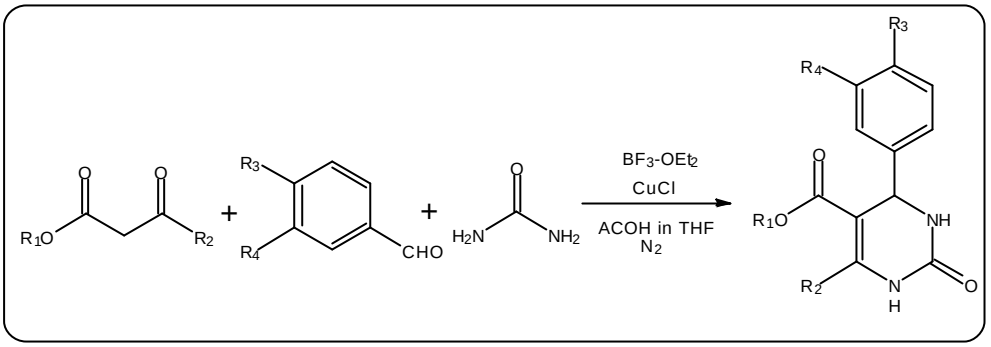
(14) Reddy Ch.et al.[44] described practical rout for the Biginelli reaction using Zirconium tetrachloride as a catalyst. Three component condensation reaction of an aromatic aldehyde, β-ketoester and urea in ethanol afford the corresponding DHPM-2-(1H)-ones in high yield.

(15) A practical and green chemistry approach towards synthesis of DHPM-2-(1H)-one without any solvent or catalyst. This method was developed by Ranu C. et al.[45] Dihydropyrimidinone was prepared from three component β-diketone, aldehyde and urea was heated under stirring at 100-105 ^{0}C afford the corresponding DHPM-2-(1H)-one in high yield (82%) and purity (> 95%).



(16) Unprecedented catalytic three-component one-pot condensation reaction described by Essa E. H. et al.[46] They set new reaction condition that was three Bilginelli components react in presence of 1.3 equivalent of BF_3-OEt_2, (10 mol %) CuCl (10 mol%) AcOH in THF reflux for 18 hr. at 60^0C, afforded corresponding DHPM-2(1H)-one.

(17) A novel one-pot condensation of an aldehyde, β-ketoester and urea was performed using aceticacid as a solvent This method described by Flokers K. et al.[47] in 1932.



(18) DHPM-2(1H)-ones were prepared in high yield by Biginelli condensation of an aldehyde, a dicarbonly compound and urea in ethanol using $Mn(OAc)_3$ as a catalyst.[48]

(20) A simple effective synthesis of DHPM-2(1H)-one derivatives, using $FeCl_3$ as catalyst from an aldehyde, β-dicarbonyl compound and urea.[29]

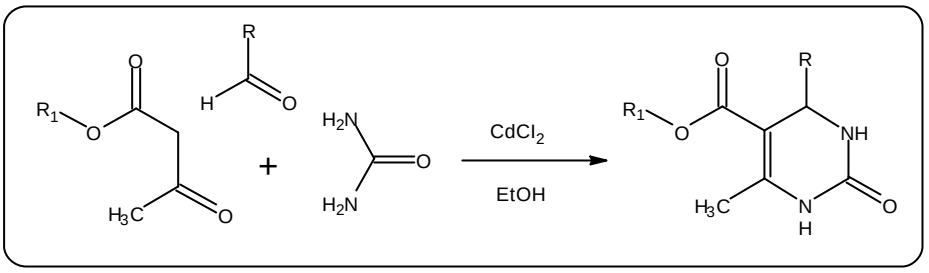
(21) K. Ramalinga et al.[49] described a simple synthesis of DHPM-2(1H)-ones derivatives using $BiCl_3$ as a catalyst from an aldehyde, β-dicarbonyl compound and urea.

(22) 3,4-DHPM-2(1H)-ones were prepared in high yield by Biginelli condensation of an aldehyde, a dicarbonyl compound and urea in ethanol using $LiClO_4$ as catalyst.[50]

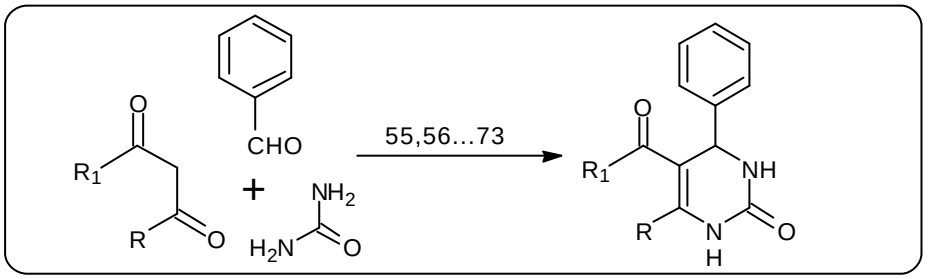
(23) 3,4-DHPM-2(1H)-one derivatives were effectively synthesized on the solution ionic liquid[51] by heating through the Biginelli three component cyclocondensation.

(24) Recently Kappe C. O.[52] demonstrated that by using neat polyphosphate ester(PPE) as reaction mediator coupled with microwave irradiation, excellent yield of variously substituted DHPMs can be obtain.

(25) Shingare M. S. et al.[53,54] examined a simple but effective procedure for Biginelli condensation reaction of an aldehyde, β–ketoester and urea using catalytic amount of cadium chloride.



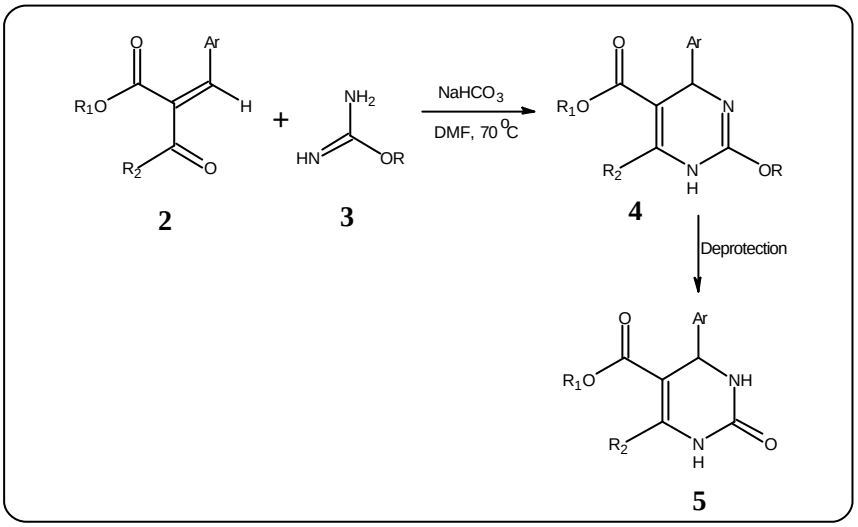
Many more new catalysts was tried on the Biginelli reaction for the yield improvement and reduce the reaction time and also for generating libraries of new molecules. There are **many new references** on this topic as per Kappe C. O. they suggested all the peoples are working in the field of yield improvement and publication point of view but some of them are devloping new molecules and test it against various disease.



55. $NiCl_2.6H_20$
56. P-TsOH, EtOH
57. $CoCl_2.6H_2O$-$LaCl_3.6H_2O$
58. Microwave(800W)
59. $NiCl_2.6H_2O$-HCl
60. $Bi(OTf)_3$.MeCN
61. NH_4Cl
62. Ferrihydrate silicarogel
63. Me_3SiCl/NaI
64. $Zn(OTf)_2$
65. $MgBr_2$
66. $Ag_3PW_{12}O_{14}$
67. $KHSO_4$
68. Con.HCl-ultrasound
69. $CdCl_2$, MeCN
70. CuCl-LiCl
71. I_2CH_3CN
72. $BiONO_3$
73. P-TSA-grinding.

Alternative Synthetic Strategies :-

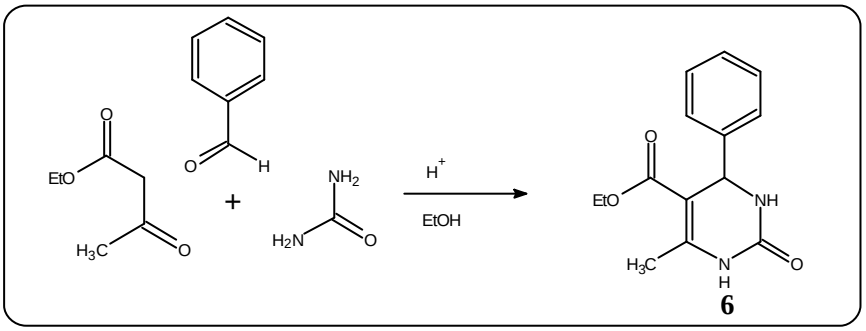
Apart from the traditional Biginelli condensation, there are only a few other synthetic methods available that lead to DHPMs. Since most of these protocols lack the experimental and conceptual simplicity of the Biginelli one-pot, one-step procedure, none of these have any significance today or can compete with the original Biginelli MCR approach. One noticeable exception is the so-called "Atwal modification" of the Biginelli reaction.[74-76] Here, an enone of type **(2)** is first condensed with a suitable protected urea or thiourea derivative **(3)** under almost neutral conditions. Deprotection of the resulting 3,4-dihydropyrimidine **(4)** with HCl or TFA/EtSH leads to the desired DHPMs **(5)**.



Multiple component reaction (MCR) : -

MCR is a reaction in which three or more reactants combine in a single reaction event to yield a product that displays features of all inputs. Multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry.[77-81] In times where a premium is put on speed, diversity, and efficiency in the drug discovery process,[82,83] MCR strategies offer significant advantages over conventional linear-type syntheses. In an ideal case, the individual building blocks are commercially

available or are easily synthesized and cover a broad range of structural variations. MCRs can provide products with the diversity needed for the discovery of new lead compounds or lead optimization employing combinatorial chemistry techniques.[78-82] The search and discovery for new MCRs on one hand,[84] and the full exploitation of already known multicomponent reactions on the other hand, is therefore of considerable current interest. One such MCR that belongs in the latter category is the venerable Biginelli dihydropyrimidine synthesis. In 1893, Italian chemist Pietro Biginelli reported on the acid catalyzed cyclocondensation reaction of ethyl acetoacetate, benzaldehyde and urea.[28] The reaction was carried out by simply heating a mixture of the three components dissolved in ethanol with a catalytic amount of HCl at reflux temperature. The product of this novel one-pot, three-component synthesis that precipitated on cooling of the reaction mixture was identified correctly by Biginelli as 3,4-dihydropyrimidin-2(1*H*)-one **(6)**.



6

Apart from a series of publications by the late Karl Folkers[85,86] in the mid 1930s, the **Biginelli reaction** or **Biginelli condensation** as it was hence forth called was largely ignored in the early part of the 20th century. The synthetic potential of this new heterocycle synthesis therefore remained unexplored for quite some time. In the 1970s and 1980s, interest slowly increased, and the scope of the original cyclocondensation reaction was gradually extended by variation of all three building blocks allowing access to a large number of multifunctionalized dihydropyrimidines of type **(4)**.[87]

Combinatorial Procedures :-

Combinatorial chemistry has rapidly become an important method for the identification and optimization of lead compounds in drug discovery.[88-92] In contrast to traditional solution organic synthesis, which often requires time-consuming purification procedures, combinatorial chemistry has been conducted almost exclusively on solid polymer supports.[93,94] Solid phase synthesis allows very simple product isolation by filtration, but this advantage at the isolation stage can be a detraction at the synthesis stage because reaction mixtures are inhomogeneous. To overcome these drawbacks, reactions of polymers that are soluble under certain conditions and insoluble under others have been introduced.[95,96] It has also been shown that imaginatively designed "traditional" solution reactions of organic molecules can provide powerful tools in combinatorial synthesis.[97,103]

The phase behavior of any reaction mixture, combinatorial or otherwise, is a crucial feature that affects the ease of purification.[104] To avoid chromatographic purification, reactions should be planned such that the phase of the desired product is different from the phases of all the other reaction components and undesired products. The "fluorous phase"[105-112] has recently been used to advantage in traditional organic synthesis. The new techniques rely on the ability of a "fluorous" (highly fluorinated) molecule to partition into the fluorous phase in a liquid-liquid extraction between an organic solvent and a fluorous solvent.[113-116]

Recently two type of combinatorial procedure for the Biginelli modification were described.

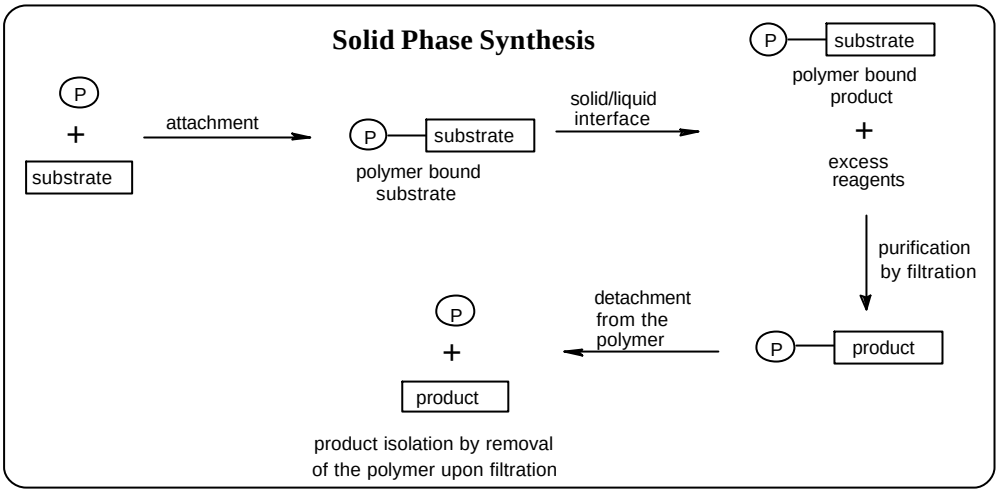
[A] Solid phase modification of Biginelli condensation

[B] Flours phase modification of Biginelli condensation

[A] Solid phase modification of Biginelli condensation :-

Solid-phase modifications of MCRs are rapidly becoming one of the cornerstones of combinatorial synthesis of small-molecule libraries.[78-80]

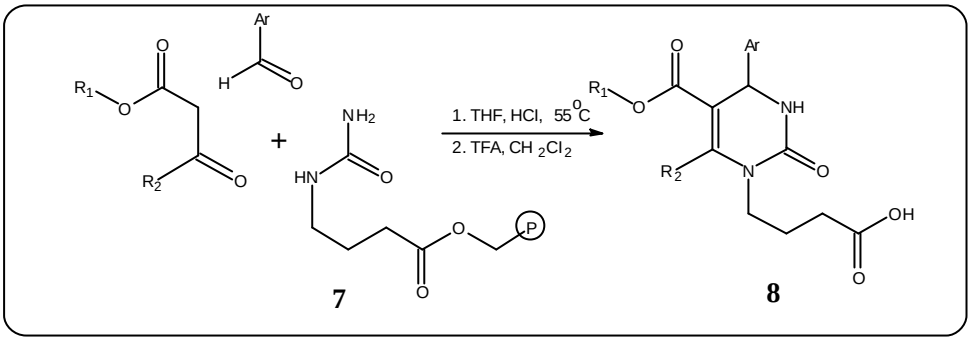
Multicomponent reactions such as the Biginelli condensation leading to heterocycles are particularly useful for the creation of diverse chemical libraries, since the combination of small-molecularweight building blocks in a single operation leads to high combinatorial efficacy.[117,118]



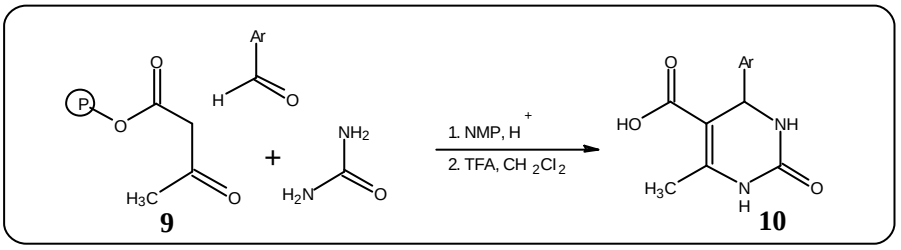
Since the experimental conditions for the traditional Biginelli reaction are rather straightforward, small libraries of DHPMs are readily accessible by parallel synthesis. Along these lines, Fre´chet and co-workers have described the generation of a 140-member single-compound DHPM library by combination of 25 aldehydes, 6 ureas/thioureas, and 7 acetoacetates or acetoamides under standard reaction conditions (EtOH/HCl).[120,121] Likewise, it has been shown that small single-compound DHPM libraries can be obtained in high yield by parallel synthesis employing the solventless microwave-enhanced variation of the Biginelli reaction.[52] The first actual solid-phase modification of the Biginelli condensation was reported by Wipf and Cunningham in 1995.[121] In this sequence, γ-aminobutyric acid-derived urea was attached to Wang resin using standard procedures.

The resulting polymer-bound urea **(7)** was condensed with excess β-ketoesters and aromatic aldehydes in THF at 55 °C in the presence of a catalytic amount of HCl to afford the corresponding immobilized DHPMs. Subsequent cleavage of product from the resin by 50% trifluoroacetic acid (TFA) provided DHPMs **(8)** in

high yields and excellent purity. The key condensation step was further studied and optimized with the aid of an automatic synthesizer demonstrating the solvent dependence of this process.[122]

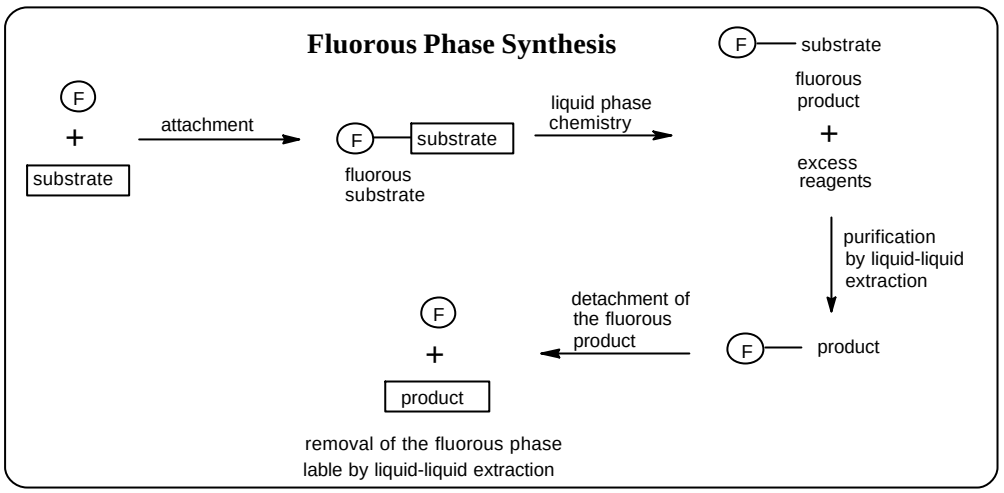


An alternative protocol, where the acetoacetate building block is linked to the solid support[71]. Thus, Biginelli condensation of Wang-bound acetoacetate **(9)** with excess aldehydes and ureas in NMP/HCl provided the desired DHPMs on solid support. Subsequent cleavage with 50% TFA furnished the free carboxylic acids **(10)** in high overall yield.[123]



[B] Flours phase modification of Biginelli condensation :-

In fluorous synthesis, the initial organic substrate is attached to a “fluorous label”, which is of sufficient structure, size and fluorine content to render the attached organic molecule fluorous.[116] One or more reactions are then conducted, and the fluorous components of the reaction are subsequently separated from all non-fluorous (organic, inorganic, solid, volatile) components by an appropriate phase separation technique. At the desired stage, the fluorous label is cleaved and the product is rendered organic. Unlike solid phase techniques, fluorous synthesis allows the routine use of standard reagents and reaction conditions. If solvents are well chosen, it is



possible to have a homogeneous solution (that is, no phase separation) at the reaction stage, but to readily induce phase separation by changing solvents at the purification stage. Furthermore, “fluorous labels” are much more robust than most polymers and linkers in current use for solid phase synthesis.

In an interesting variation of this protocol, the Biginelli reaction was also adapted to fluorous-phase conditions by the Wipf and Curran groups.[124,125] In fluorous synthesis, an organic molecule is rendered soluble in fluorocarbon solvents by attachment of a suitable fluorocarbon group (“fluorous tag”). Fluorocarbon solvents are usually immiscible with organic solutions, and fluorous molecules partition out of an organic phase and into a fluorous phase by standard liquid-liquid extraction. At the desired stage of the synthesis, the fluorous label is cleaved and the product is rendered “organic” again.[124] In the fluorous Biginelli reaction, the fluorous urea derivative **(11)** was prepared by attachment of a suitable fluorous tag to hydroxyethylurea. The fluorous urea **(11)** was then condensed with 10 equivelent each of the corresponding acetoacetates and aldehydes in THF-benzotrifluoride (BTF) containing HCl. After extraction of the fluorous DHPMs with fluorous solvent (perfluorohexanes, FC-72), desilylation with tetrabutylammonium fluoride (TBAF) followed by extractive purification provided the “organic” Biginelli products DHPMs

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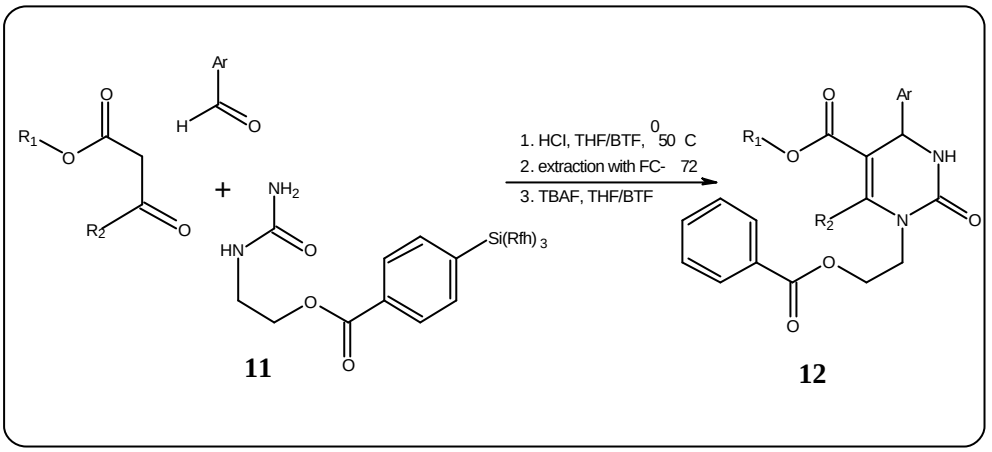


(12) in good overall yields. Considering the simple experimental techniques used in this fluorous chemistry, automation should be feasible, thus allowing the preparation of DHPM libraries.[125]

By employing any of the solid-phase synthesis methods described above, libraries of DHPMs can be generated in a relatively straightforward fashion. Biginelli products are therefore contained in many commercially available small molecule libraries or compound collections and have undoubtely been subjected to many high-throughput screening (HTS) processes. However, all of these products would still be racemic, and therefore screening will not address possible enantioselective effects on molecular activity.

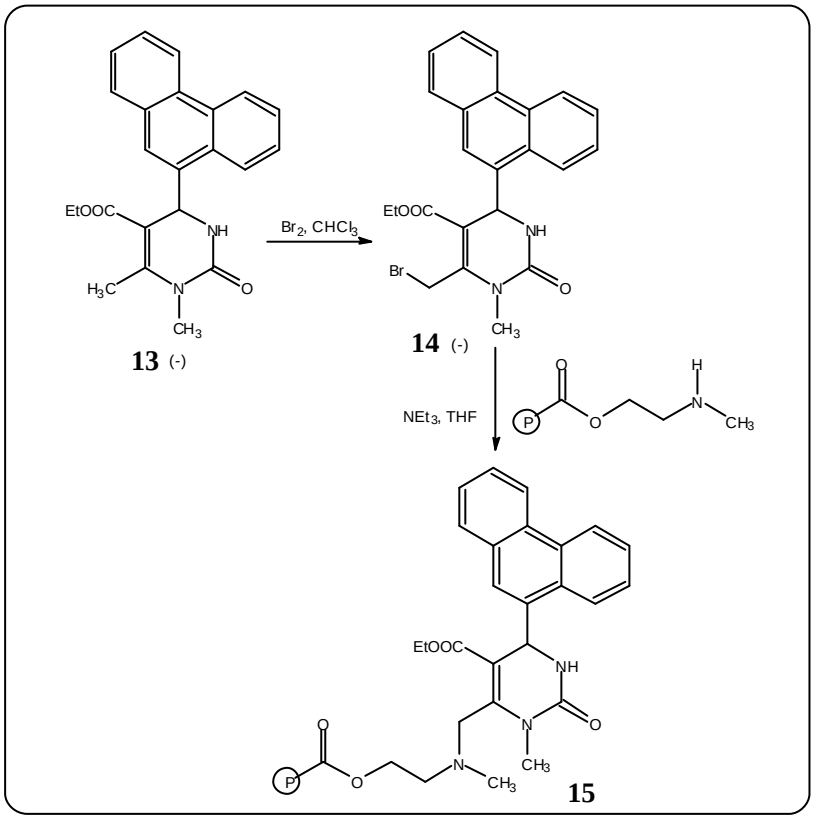
Enantiomerically Pure Dihydropyrimidines :-

Dihydropyrimidines of the Biginelli type are inherently asymmetric molecules, and the influence of the absolute configuration at the stereogenic center at C4 on biological activity is well documented.[126-131] In SQ 32926 **(11)**, for example, it is exclusively the (*R*)-enantiomer that carries the therapeutically desired antihypertensive effect.[126] In other DHPM analogues, individual enantiomers were demonstrated to have opposing pharmacological activities.[131] Access to enantiomerically pure DHPMs is therefore of considerable interest and a prerequisite

for the development of any drugs in this field.

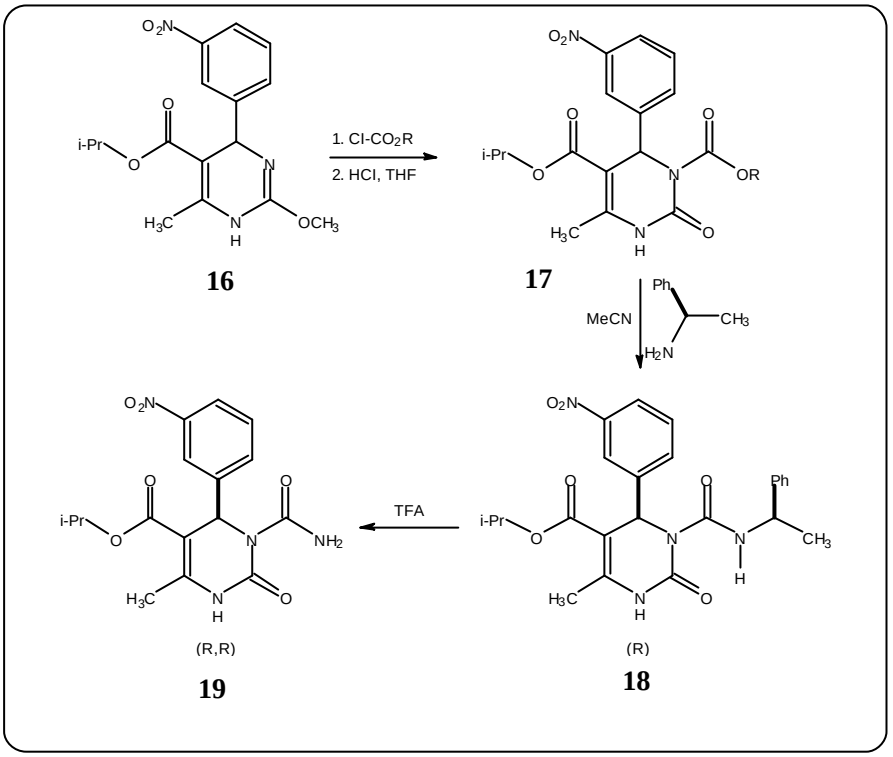
In a recent the chromatographic enantioseparation of DHPM derivatives accomplished by using a variety of commercially available chiral stationary phases (CSPs) in normal- and reversed-phase analytical HPLC.[132] Kappe C. O. and Co-workers[133] tested that out of 29 diverse racemic DHPM analogues, all but one was separated on at least one of the eight CSPs with separation coefficients α ranging from 1.08 to 8.67.

In subsequent work, Frechet and co-workers reported the separation of DHPMs on a standard Pirkle-type 3,5-dinitrobenzoylated CSP and the "reciprocal" preparation of a π-basic DHPM-based CSP.[120,121] Using a combinatorial approach toward the recognition of chirality, out of a library of 108 racemic DHPMs, the 4-(9-phenanthryl) derivative **(13)** was identified as a lead structure with a separation coefficient of α=5.2 on a Pirkle-type CSP.



13 (-) **14** (-) **15**

The chiral separation of DHPMs by capillary electrophoresis (CE) using quaternary ammonium-β-cyclodextrin as chiral buffer additive has also been reported.[134] A preparatively useful synthetic approach to the enantiomerically pure antihypertensive agent (*R*)-SQ 32926 **(19)** was disclosed by Atwal et al.[126]



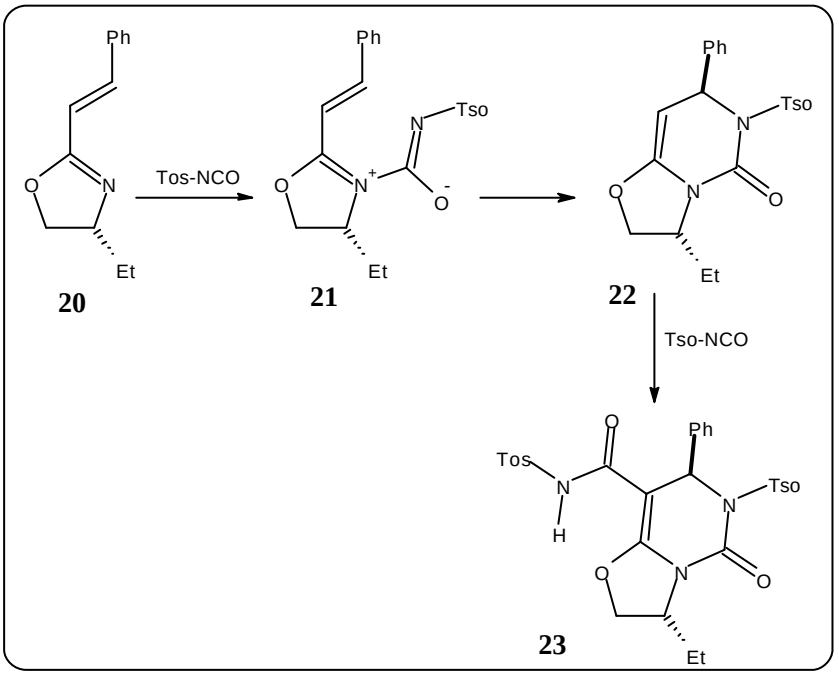
Similar strategies have been used to obtain a number of pharmacologically important DHPM derivatives in enantiomerically pure form.[126,127,129] Kappe C.O. et al.[133] developed a biocatalytic strategy toward the preparation of enantiopure (*R*)- and (*S*)-SQ 32926 **(19)**. The key step in the synthesis is the enzymatic resolution of an N3-acetoxymethyl-activated dihydropyrimidone precursor by Thermomyces lanuginosus lipase.[135]

A critical point in every preparation of enantiomerically pure materials, regardless of the method, is the assignment of absolute configuration. For the DHPM series, a simple protocol for absolute configuration assignment based on the combination of enantioselective HPLC and circular dichroism (CD) spectroscopy

has been developed.[136]

By comparison of the characteristic CD spectra of individual DHPM enantiomers with reference samples of known absolute configuration, the absolute configuration of 4-aryl-DHPMs, such as monastrol (**8**),[137] or SQ 32926 (**5**),[135] could be established. The enantiomers were obtained by semipreparative HPLC separation of racemic DHPMs on chiral stationary phases.[135] The characteristic CD activity of the enamide chromophor around 300 nm allows the assignment of absolute configuration in this series of dihydropyrimidine derivatives.[136]

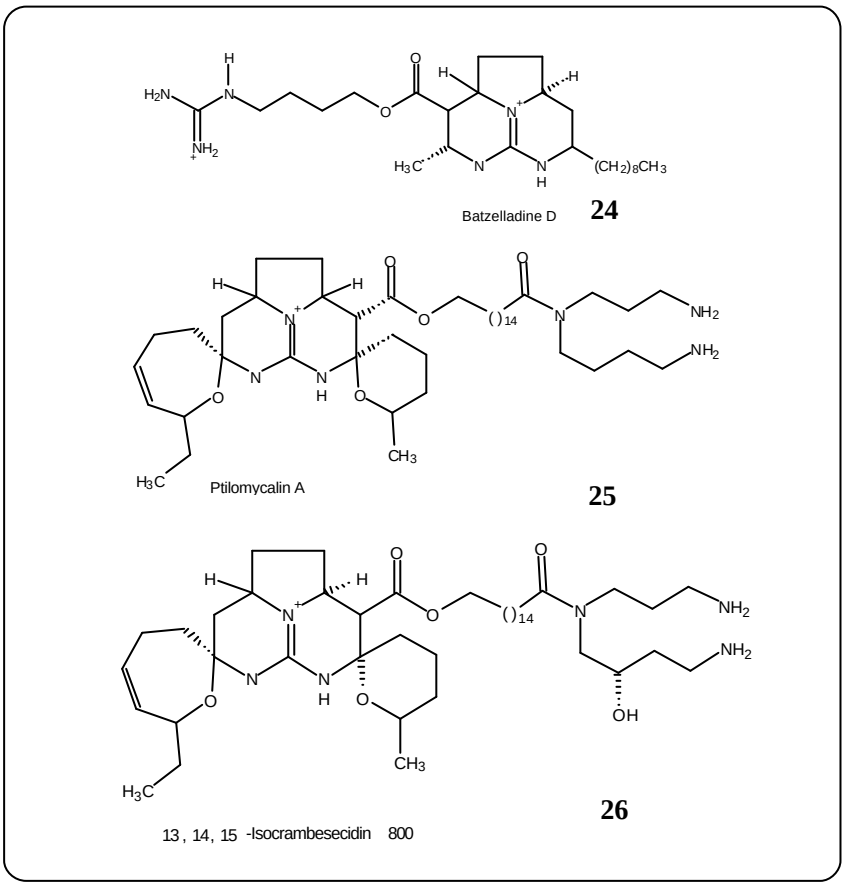
As mentioned above, a generally applicable asymmetric synthesis of DHPMs has not been reported yet. However, fused DHPMs of type **(23)** have recently been obtained by Elliott et al.[138] in diastereomerically pure form by asymmetric hetero-Diels-Alder addition of chiral alkenyloxazolines **(23)** with isocyanates. Mechanistic investigations suggest that the reaction proceeds in a stepwise manner (**20** ⟶ **21** ⟶ **22** ⟶ **23**).[139] It remains to be seen if this strategy can be adapted toward a more general synthesis of enantiopure DHPMs.



Efforts to develop a practical asymmetric version of the Biginelli reaction itself have failed so far. While chiral acetoacetates, e.g., (-)-menthyl acetoacetate, show no diastereoselectivity at all,[140] chiral aldehydes derived from carbohydrates apparently can induce chirality at C4 of the pyrimidine ring.[141]

Natural Product Synthesis

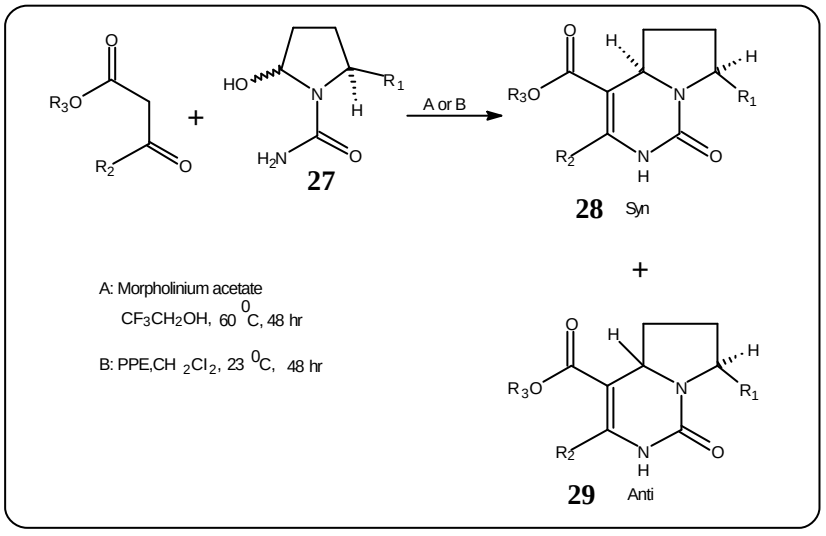
Over the last 10 years, a variety of structurally novel and complex guanidine alkaloids have been isolated from marine sources, such as the Caribbean sponges *Ptilocaulis spiculifer* or *Batzella* sp.[142] Among these are the batzelladine alkaloids A-I **(24)**, ptilomycalin A **(25)**, and the alkaloids crambescidin A, 800, and 816.[142] A closely related alkaloid, 13,14,15-isocrambescidin 800 **(26)** was subsequently isolated from the Mediterranean sponge *Crambe crambe*.[142]



Although several strategies to assemble the tricyclic or pentacyclic cores of these guanidinium alkaloids have been realized, one of the most efficient protocols relies on an intramolecular Biginelli condensation as the key step. In fact, the "tethered Biginelli strategy" developed by Overman and co-workers has so far proven to be the only method that has allowed the enantioselective total synthesis of alkaloids in this family.[143-149]

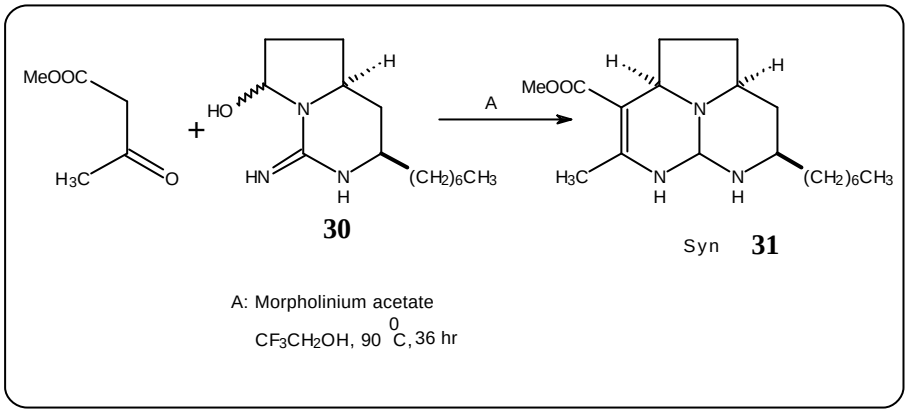
When typical Knoevenagel conditions (morpholinium acetate) were employed, cis stereoselection was observed (*syn*-**28**). In contrast, when the condensation was carried out in the presence of polyphosphate ester (PPE),[150] trans stereoselection was observed (anty-**29**).[143] The tricyclic guanidine *syn*-**(31)** was obtained in 82% isolated yield and is identical with the methanolysis product of the naturally occurring batzelladine B.[151]

Similar strategies based on enantioselective Biginelli reactions were employed in the total synthesis of batzelladine D (**24**),[145] ptilomycalin A (**25**),[146,149] 13,14,15-isocrambescidin 800 (**26**),[147,148] 13,14,15-isocrambescidin 657,[148] crambescidin 657,[149] and crambescidin 800.[149]



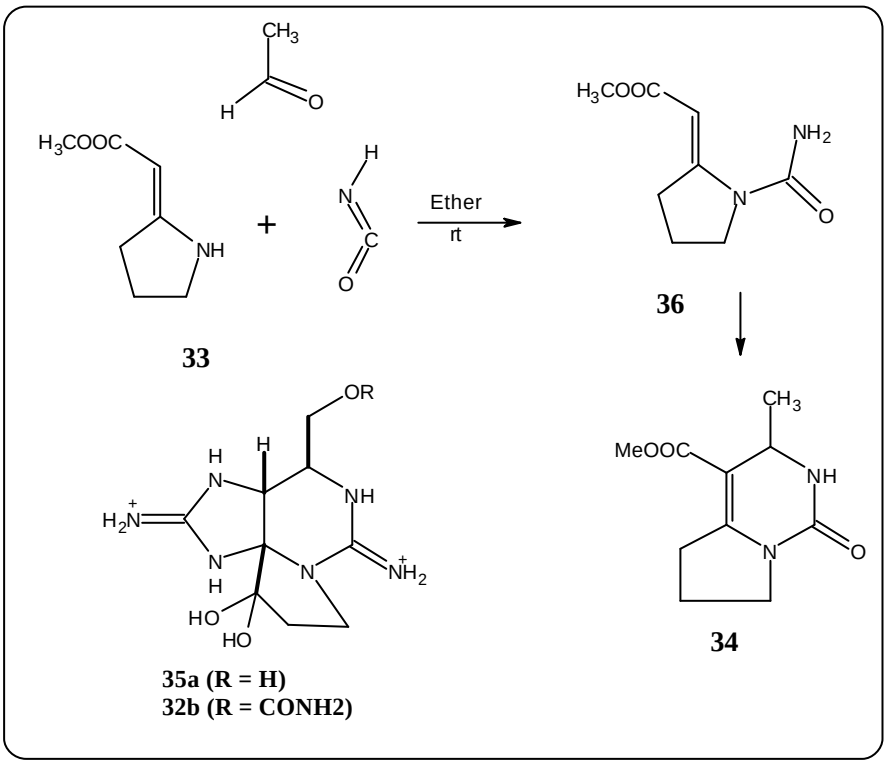
In the context of an enantioselective total synthesis of the highly potent neurotoxin saxitoxin (**32b**), the Kishi group has developed a novel trimolecular

cyclization reaction that is somewhat reminiscent of the Biginelli condensation.[152,153,154]



30 **31**

From the mechanistic point of view, an ureidocrotonate species of type **(36)** has been discussed as an intermediate in this trimolecular cyclization.[155] It is interesting to note that corresponding enamides have also been considered as intermediates in the classical Biginelli reaction.[156,157]

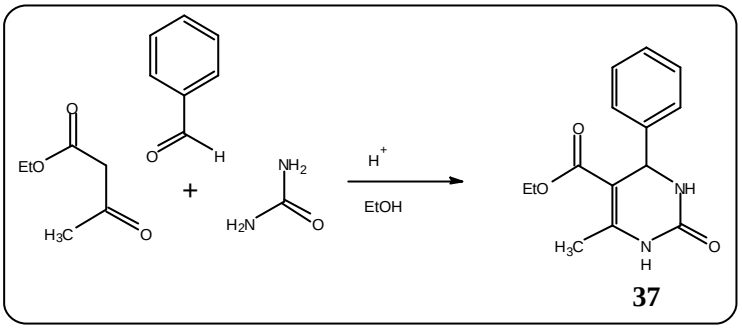


33 **36** **34**

35a (R = H)
32b (R = CONH2)

MECHANISTIC STUDIES :

In 1893 Biginelli reported the first synthesis of dihydropyrimidines of type **(37)** by a simple one-pot condensation reaction of ethyl acetoacetate, benzaldehyde, and urea.[28]



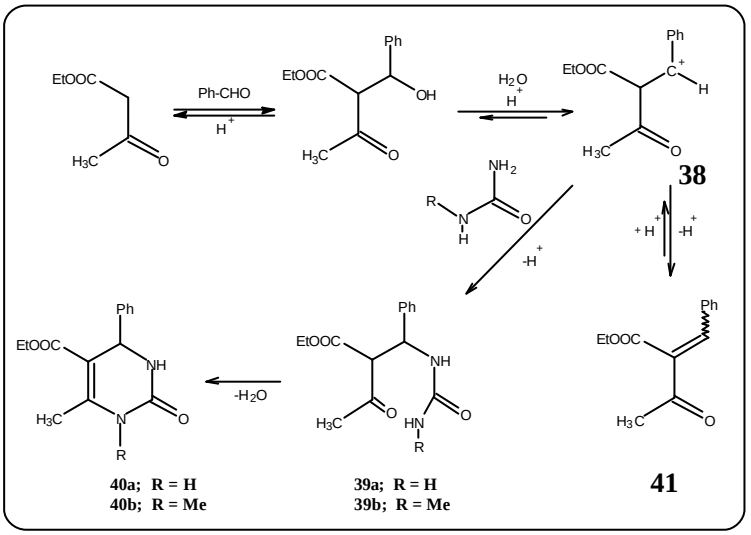
37

Despite the importance and current interest in dihydropyrimidines of type **(37),** the mechanism of the classical three-component Biginelli condensation has not been elucidated with certainty and remains disputed.[87] Early work by Folkers and Johnson suggested that *N,N*- benzylidenebisurea, *i.e.* the primary bimolecular condensation product of benzaldehyde and urea, is the first intermediate in this reaction.[158] Later, Sweet and Fissekis have proposed a different mechanism postulating that carbenium ion **(38)**, produced by an acid-catalyzed aldol reaction of benzaldehyde with ethyl acetoacetate, is the key intermediate and is formed in the first and limiting step of the Biginelli reaction.[159]

To decide which of the two fundamentally different mechanistic proposals is correct Kappe C. O.[157,158] carried out a detailed reinvestigation of the mechanism of the Biginelli condensation using ^{1}H and ^{13}C NMR spectroscopy to identify possible intermediates. To be able to monitor all reactions by ^{1}H and ^{13}C NMR spectroscopy, it is very likely that this three component condensation proceeds via one of the three possible bimolecular reaction pathways from the urea/aldehyde/acetoacetate system.

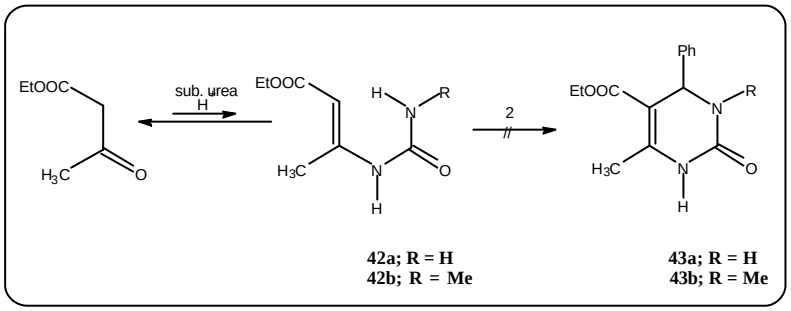
The "carbenium ion mechanism" was proposed by Sweet and Fissekis,[159] who investigated the reaction in 1973 and suggested that an acid-catalyzed aldol condensation is the first and limiting step of the Biginelli condensation. It was proposed that under acid catalysis benzaldehyde and ethyl acetoacetate would react in an aldol-type fashion to produce the corresponding aldol, which dehydrates in the presence of acid to the resonance-stabilized carbenium ion **(38)**.[159,161]

Interception of cation **(38)** by urea or *N*-methylurea then produces ureides **(39),** which ultimately cyclize to the Biginelli products **(40)**.[159] The main argument for the proposed mechanism made by the authors[159] relates to the fact that acid-catalyzed treatment of independently prepared enone **(41)** with *N*-methylurea also produced pyrimidine in moderate yield.[159]



According to Sweet and Fissekis, protonation of enone **(41)** regenerates the carbenium ion intermediate **(38),**[161] which then can react with urea or *N*-methylurea. It was also considered important that in the reaction of enone **(41)** with *N*-methylurea only the *N*1-methyl derivative **(40b)** was produced and not the *N*3-substituted isomer,which corresponds to the regiochemical outcome observed in the three component Biginelli reaction of ethyl acetoacetate, benzaldehyde, and *N*-methylurea.[87,162]

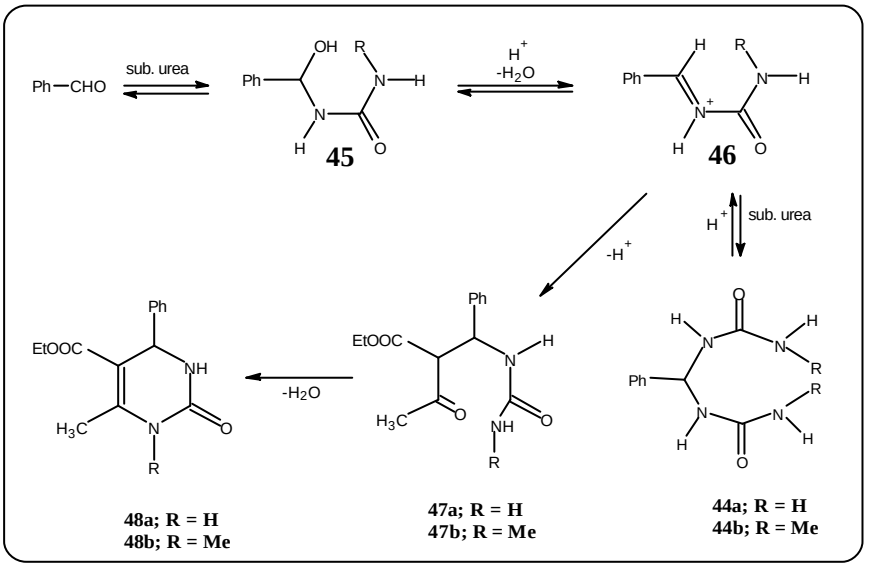
The so-called “ureidocrotonate mechanism” was already considered by Folkers and Johnson[158] but was ruled out as a mechanistic pathway since the bimolecular condensation product of ethyl acetoacetate and urea, *i.e.* ureidocrotonate **(42a)**,[164] was shown to rapidly hydrolyze under the typical Biginelli reaction conditions (EtOH, HCl).[158] Since the fact that ureidocrotonate **(42a)** is sensitive to hydrolysis does not exclude this intermediate for the Biginelli reaction. The independently prepared[164-166] enamides **(42a**,**b)** were shown to rapidly hydrolize in CD_3OH when catalytic amounts of acid (and water) were present While ureidocrotonates **(42a**,**b)** can be prepared from diketones and substitued urea under strictly anhydrous conditions, *i.e.* by allowing a mixture of diketone and substituted urea to react in a desiccator over concentrated H_2SO_4 for several days,[164-166] it is evident that under Biginelli reaction conditions the equilibrium is far on the acetoacetate/urea side.



Another argument against the involvment of an ureidocrotonate intermediate relates to the fact that *N*-methylurea reacts with ethyl acetoacetate to furnish exclusively regioisomer **(42b)** bearing the *N*-methyl substituent at the terminal amino group.[165,166] The formation of a Biginelli dihydropyrimidine in a 5 + 1 cyclocondensation manner from **(42b)** and benzaldehyde would be expected to lead to the *N*3-substituted Biginelli product **(43b)**,[167] which is observed neither in the three component Biginelli reaction[87,159,162] nor from the reaction of ureide **(42b)** with benzaldehyde under Biginelli conditions.

Finally, Kappe C. O. considered the original mechanistic proposal made by Folkers and Johnson,[158] who suggested that the first step in the three-component Biginelli condensation is the reaction of benzaldehyde with urea. When benzaldehyde and urea were reacted under typical Biginelli conditions (CH_3OH/HCl) at room temperature, the anticipated condensation product bisureide **(44a)**[168-170] started to precipitate from the solution within 15-20 min. Bisureide **(44a)** was also formed when equimolar amounts of the two components were employed, and the analogous condensation product **(44b)**[171,172] was produced when *N*-methylurea was used instead of urea.

However, when these reactions were carried out in the presence of ethyl acetoacetate under identical reaction conditions, bisureides **(44a**,**b)** were not formed, but dihydropyrimidines **(40a**,**b)** started to precipitate slowly from the reaction mixture within 1-2 hr. (complete conversion took 2-3 days).



The addition of ureas to benzaldehyde leads to *N*-(1-hydroxybenzyl)-ureas of type **(45)** via standard nucleophilic addition. Although this is likely to be an equilibrium reaction, "hemiaminals" **(45)** are expected to undergo rapid dehydration in the presence of acid to a carbenium ion which may be formulated as a highly

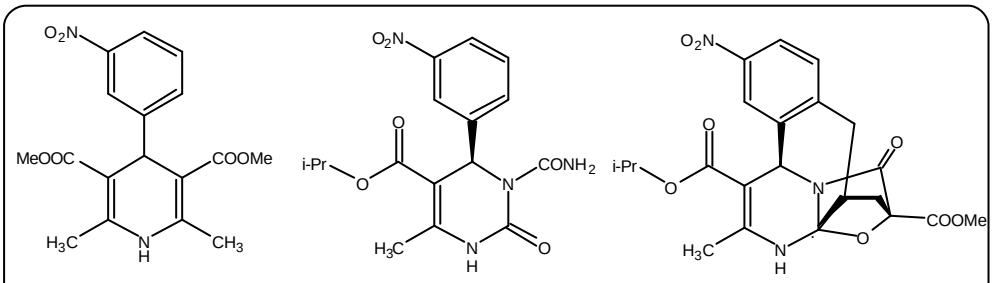
reactive *N*-acyliminium species, *i.e.* **(46)**. In the absence of the 1,3-dicarbonyl compound a second equivalent of urea is added to furnish bisureides **(44a,b)** which due to their low solubility[168-172] precipitate from the reaction mixture. However, if ethyl acetoacetate is present in the reaction medium, iminium ion **(46)** is intercepted by the 1,3-dicarbonyl compound, possibly through its enol tautomer, to furnish intermediates **(47a,b)** which then cyclize to the Biginelli compounds **(48a,b)**. Monitoring the formation of bisureides **(44a,b)** from aldehyde and urea by ^{1}H NMR (CD_3OH, HCl) did not allow the observation of any intermediates, *e.g.* **(45)**, in this process. The first addition step is the rate-determining (slow) step and that both the subsequent acid-catalyzed dehydration (**45** → **46**) and the addition of a second equivalent of urea to the iminium ion (**46** → **44**) are fast steps, therefore not allowing **(45)** to accumulate.

Finally the original mechanistic proposal put forward by Folkers and Johnson in 1933,[158] involving an aldehyde-urea condensation product as key intermediate in the Biginelli condensation is essentially correct. The first step in this mechanism evidently involves the acid-catalyzed formation of an *N*-acyliminium ion precursor of type **(46)** from an aldehyde and urea component. In the case of amides and carbamates, this reaction pathway is well-established,[173,174] and at least one example exists for ureas.[175,176] The second step can be regarded as an addition of a π-nucleophile, *i.e.* the enol tautomer of acetoacetate to the electrondeficient *N*-acyliminium species **(46)**. Additions of π-nucleophiles to iminium species are very well-known and have proven to be valuable synthetic transformations in target-oriented synthesis.[173,174] Importantly, several examples of this type of reaction involving 1,3-dicarbonyl compounds and urea-derived *N*-acyliminium ions yielding dihydropyrimidines of type **(37)** are reported in the literature,[175,176] providing additional support for this mechanism.

THERAPEUTIC IMPORTANCE :-

Calcium ion plays a vital role in a large number of cellular processes, including excitation-contraction and stimulus-secretion.[177,179] The regulation of the intracellular concentration of this ion makes possible the control of such Ca^{2+}-dependent processes. One means of accomplishing this is by the use of agents known as calcium channel antagonists, which inhibit the movement of calcium through certain membrane channel.[178,180,181]

In recent years interest has also focused on aza-analogs such as dihydropyrimidines of type **(50)** which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators.[182-188] Over the past few years several lead-compounds were developed (*i.e.* SQ 32,926)[127,185,186] that are superior in potency and duration of antihypertensive activity to classical dihydropyridine drugs, and compare favorable with second-generation analogs such as **amlodipine** and **nicardipine**.[127,185] These inherently asymmetric DHPM derivatives are not only very potent calcium channel modulators, but also have been studied extensively to expand the existing structure-activity relationships and to get further insight into molecular interactions at the receptor level.[182-188]



49 **50**, SQ 32926 **51**

DHP calcium channel antagonists (*e.g.* **49**, nifedipine) are flexible molecules, in which the C4-aryl moiety and the C3/C5 ester substituents can rotate, and the conformation of the 1,4-dihydropyridine ring can change.[189] Despite many studies on

the structure-activity relationships for DHPs and DHPMs with respect to calcium channel antagonist-agonist modulation, there still remains debate on the exact stereochemical/ conformational requirements for activity.[187-191] It was recently proposed that calcium channel modulation (antagonist *vs*. agonist activity) is dependent on the absolute configuration at C4, whereby the orientation of the 4-aryl group (*R*- versus *S*-enantiomer) acts as a "molecular switch" between antagonist and agonist activity.[187,188] In the receptor-bound conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat-like dihydropyridine ring, with the 4-aryl substituent (X) prefering the synperiplanar (sp) orientation relative to C4-H (Fig. 1).[187,188]

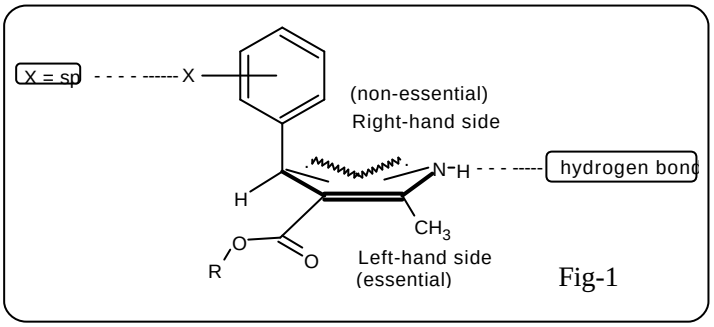


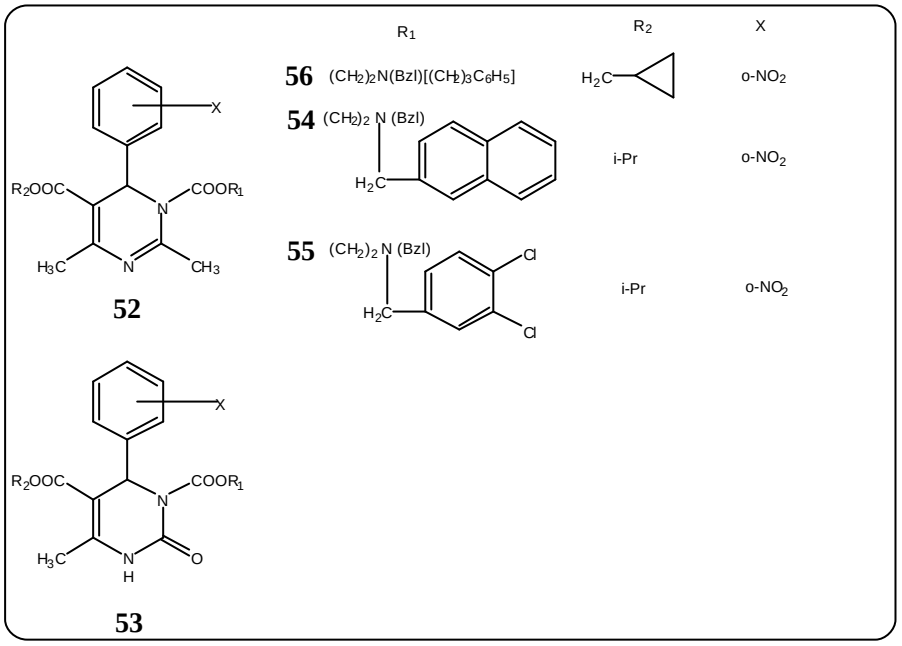
Fig-1

A cis-carbonyl ester orientation (with respect the C5=C6 bond) was also found mandatory for calcium channel modulatory activity, whereas the right-hand side of the dihydropyridine ring was proposed non-essential,[187,188] providing a rationale for the similar pharmacological profile observed for DHPs and DHPMs.

Kappe C. O. et al.[192] synthesize the polycyclic DHPM derivative **(51)** that represents a conformationally rigid analog of SQ 32,926[185], "frozen" in the putative bioactive conformation shown in Fig. 1. All structural changes on**(50)** are made on the non-essential right hand side of the molecule, thereby not interfering with the receptor-sensitive groups on the left-hand side.

Hidetsura Cho et al.[182] synthesized the novel calcium antagonists 3-N-substituted-3,4-dihydropyrimidines **(52)** and 3-N-substituted-dihydropyrimidin- 2(1H)-ones **(53)** were regioselectively synthesized in good yields. Compounds **(54)** and **(55)** exhibited

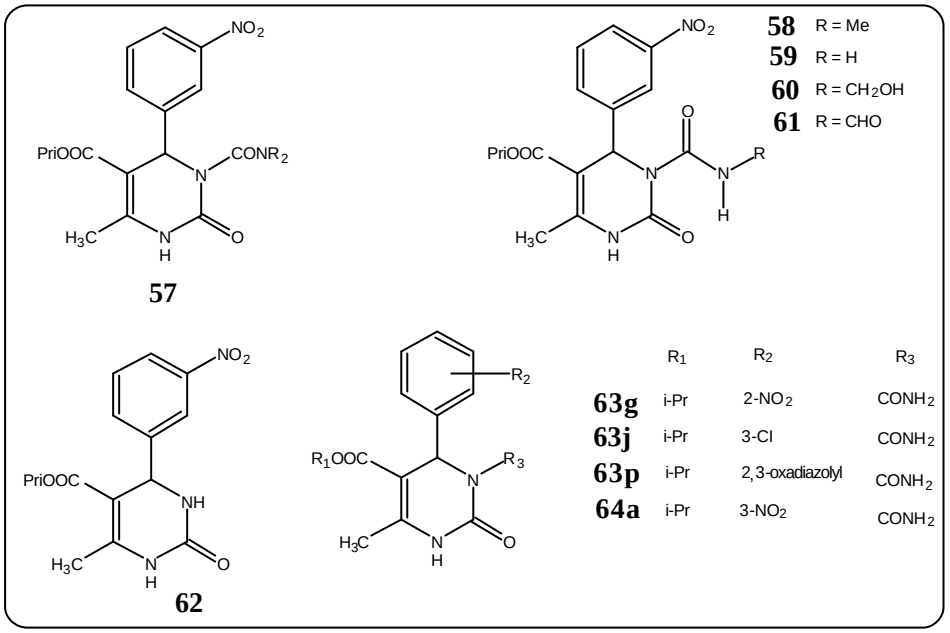
not only more potent and longer lasting vasodilative action but also a hypotensive activity with slow onset as compared with dihydropyridines. Moreover, some dihydropyrimidines **(56)**, **(54),** and **(55)** were weaker in blocking atrioventricular conduction in anesthetized open-chest dogs and less toxic than the dihydropyridines.



Atwal K. S. et al.[185] described that in order to explain the potent antihypertensive activity of the modestly active (ICw = 3.2 pM) dihydropyrimidine calcium channel blocker **(57),** they carried out drug metabolism studies in the rat and found **(5)** is metabolized to compounds **(58-62)**. Two of the metabolites, **(58)** (ICw = 16 nM) and **(59)** (ICw = 12 nM), were found to be responsible for the antihypertensive activity of compound **(57).** Potential metabolism of **(58)** into **(59)** *in vivo*. Structure-activity studies aimed at identifying additional aryl-substituted analogues of **(59)** led to **(63g,j,p)** with comparable potential *in vivo*, though these compounds were less potent than **(59)** *in vitro*.

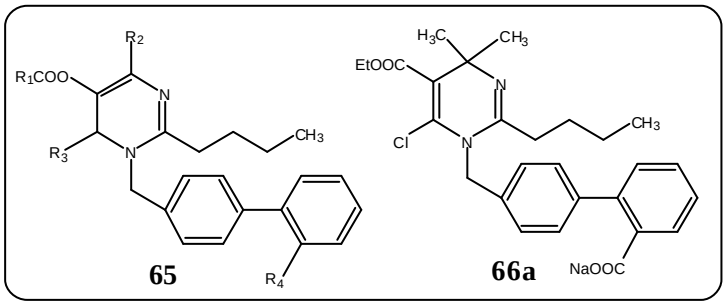
The results demonstrate that the active R-(-)-enantiomer **(64a)** of **(59)** is both more potent and longer acting than nifedipine as an antihypertensive agent in the SHR. The *in vivo* potency and duration of **(64a)** is comparable to the long-acting

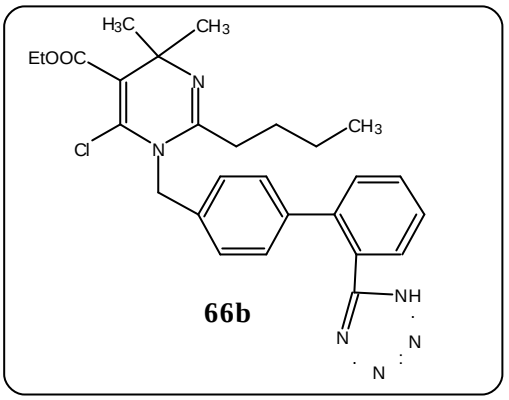
dihydropyridine amlodipine.



The pioneering discovery of the angiotensin converting enzyme (ACE) inhibitor captopril as an antihpertensive agtent,[193] the renin-angiotensin system has beccome an imprtent target for further drug discovery.[194-196] Due to the commercial sucess of ACE inhibitors, a large effort in medicinal chemistry has cotinued to focus on further manipulation of this system. Renin inhibitors[197] and angiotensin II (AII) antagonists[198] have enjoyed considerable popularity among pharmaceutical scientists. However, the use of both these classes agents as potential cardiovascular drugs had been hampered by their peptidic nature, usually responsible for poor oral bioavailability and limited half-life.

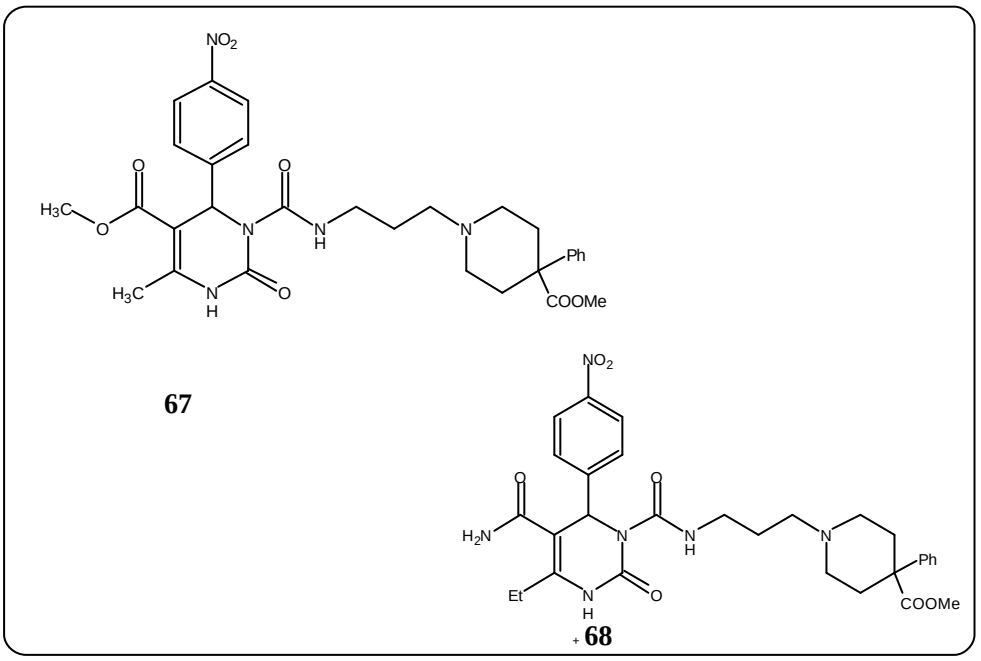
Efforts of Atwal K. S. et al.[199] in this area have resulted in the discovery of dihydropyrimidines **(65)** and **(66a,b)** as plotent AII receptor antagonists





66b

Dhanapalan N. et al.[200] prepared dihydropyrimidinones such as compound **(67)** exhibited high binding affinity and subtype selectivity for the cloned human α_{1a} receptor. Systematic modifications of **(67)** led to identification of highly potent and subtype-selective compounds such as (+)-**(68)** and (+)-**(69)**, with high binding affinity (K_1) 0.2 nM) for α_{1a} receptor and greater than 1500-fold selectivity over α_{1b} and α_{1d} adrenoceptors. The compounds were found to be functional antagonists in human, rat and dog prostate tissues. Compound (+)-**(69)** exhibited excellent selectively to inhibit intraurethral pressure (IUP) as compared to lowering diastolic blood pressure (DBP) in mongrel dogs (*K*b(DBP)/*K*b(IUP))= 40) suggesting uroselectivity for α_{1a}-selective compounds.



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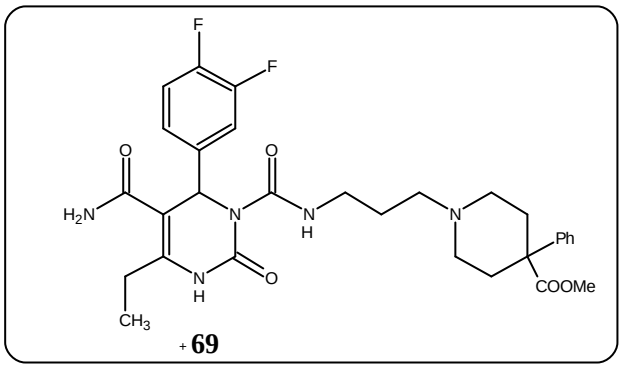
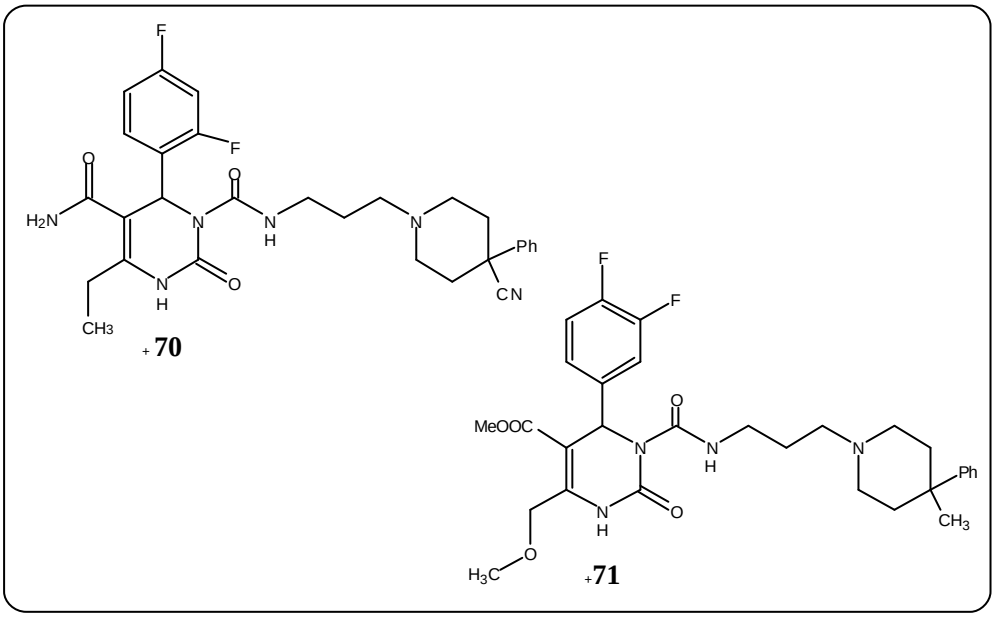
68



+ **69**

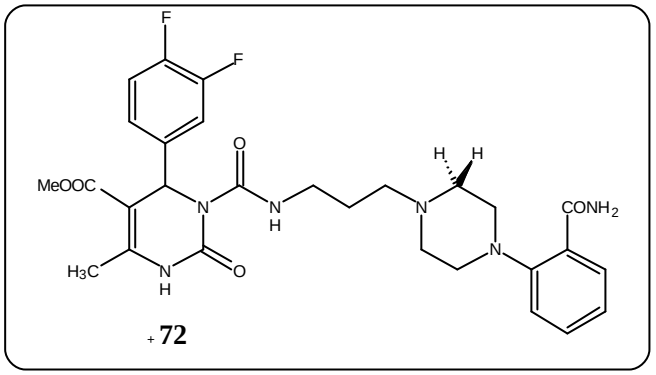
T. G. Muralidhar et al.[201] have synthesized several DHPM-one analogues among this (+)-**(70)** and (+)-**(71)** give excellent selectivity (>880-fold) over α_{1b} and α_{1d} also showed good selectivity over several other recombinant human G-protein coupled receptors. These compounds showed good functional potency in isolated human prostate tissues, with *K*bs comparable to their *in vitro* α_{1a} binding data. In addition, compound (+)-**(70)** also exhibited good uroselectivity (DBP *K*b/ IUP *K*b > 20-fold) in the *in vivo* experiments in dogs.



+ **70** + **71**

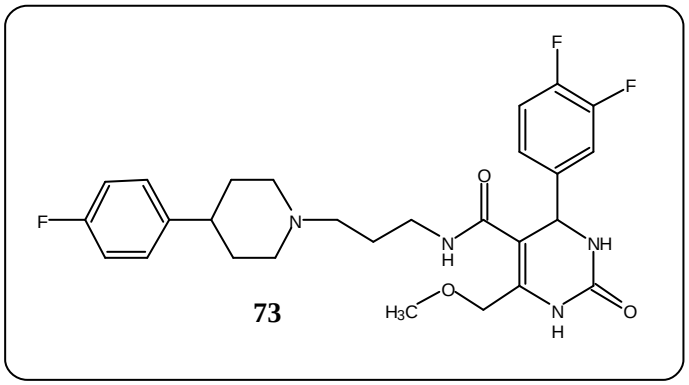
Bharat L. et al.[202] identify that compound **(+)-(72)** was a lead compound with a binding and functional profile comparable to that of (+)-**(71)**. The putative metabolite

2-carboxamidophenylpiperazine has negligible affinity for the μ-opioid receptor.



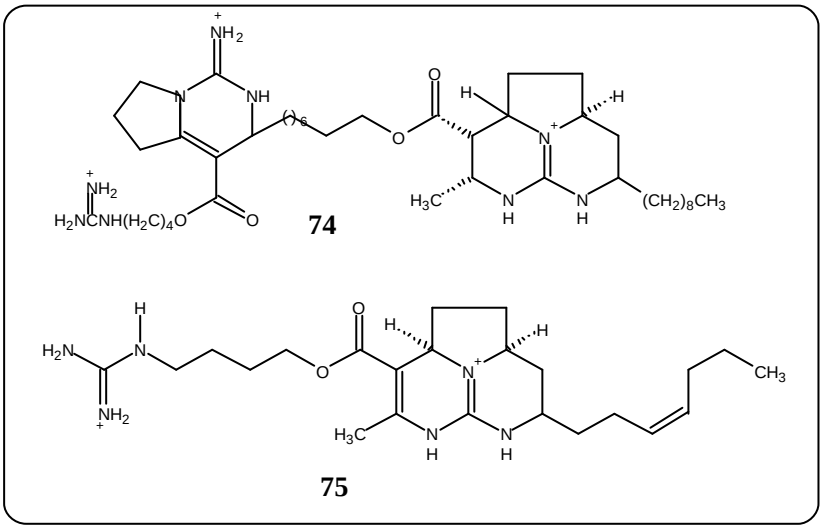
72

James C. et al.[203] explores 4-aryldihydropyrimidinones attached to an aminopropyl-4-arylpiperidine via a C-5 amide as selective α_{1a} receptor subtype antagonists. In receptor binding assays, these types of compounds generally display *K*1 values for the α_{1a} receptor subtype <1 nM while being greater than 100-fold selective versus the α_{1b} and α_{1d} receptor subtypes. Many of these compounds were also evaluated *in vivo* and found to be more potent than terazosin in both a rat model of prostate tone and a dog model of intra-urethral pressure without significantly affecting blood pressure. While many of the compounds tested displayed poor pharmacokinetics, compound **(73)** was found to have adequate bioavailability (>20%) and half-life (>6 h) in both rats and dogs. Due to its selectivity for the α_{1a} over the α_{1b} and α_{1d} receptors as well as its favorable pharmacokinetic profile, **(73)** has the potential to relieve the symptoms of BPH without eliciting effects on the cardiovascular system.



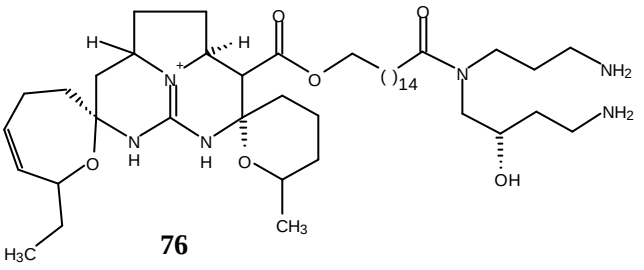
73

Several recently isolated marine alkaloids with interesting biologicalactivities alos contain dihydropyrimidinone nucleous. Frederick C. et al.[204] desccribed that a novel class of polyguanidine alkaloids isolated from the red Caribbean sponge *Batzella* sp.[205,206] Nine members of this group have now been identified by Smith-Kline Beecham scientists from a program searching for modulators of protein-protein interactions. The most complex batzelladine alkaloids, exemplified by batzelladine A **(74)** have two polycyclic guanidine units, while batzelladines C, D, and E **(75)** display a single tricyclic guanidine moiety. A decahydro- or octahydro-5,6,8b-triazaacenaphthalene is the common structural feature of the batzelladines, with these tricyclic units occurring with both the *syn* and *anti* stereorelationships of the angular hydrogens that flank the pyrrolidine nitrogen.[205-207] Batzelladines A **(74)** and B are micromolar inhibitors of binding of the HIV envelope protein gp-120 to the human CD4 receptor, while at similar concentrations batzelladines F-I induce dissociation of the protein kinase called $p56^{lck}$ from CD4.[205,206,208-214]

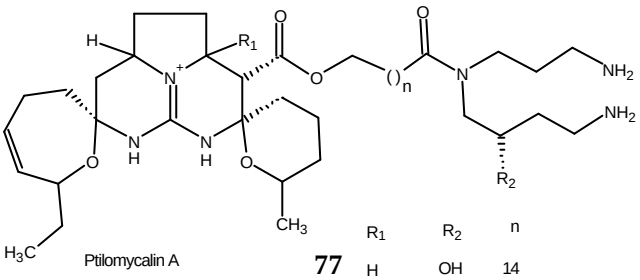


Crambe crambe, a bright red encrusting sponge commonly found at shallow depths along the rocky coast of the Mediterranean, is a rich source of structurally novel, bioactive alkaloids.[215] Rinehart and co-workers[216] and later Braekman and his group,[217,218]

described a series of complex guanidinium alkaloids, including 13,14,15-isocrambescidin 800 **(76)**, crambescidin 800 **(77)**, crambescidin 844 **(78)** and crambescidin 816 **(79)**, from *C. crambe*. The related alkaloid, ptilomycalin A **(80)**, was reported earlier by Kashman, Kakisawa and co-workers from sponges collected in the Caribbean and Red Sea.[219-221] Ptilomycalin A[219-222] and several of the crambescidins[216-218] show substantial antitumor, antiviral and antifungal activities.[216-222] As a result of its low abundance, 13,14,15-isocrambescidin 800 has not been extensively screened, although it is reported to be less cytotoxic to L-1210 cells than other crambescidins.[223] The defining structural feature of the crambescidin alkaloids is a pentacyclic guanidine linked by a straight chain ω-hydroxycarboxylic acid spacer to a spermidine or hydroxyspermidine unit.



76



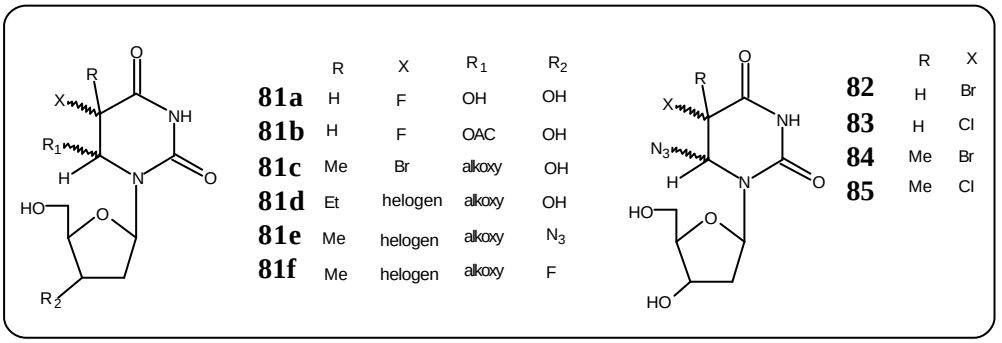
Ptilomycalin A

	R_1	R_2	n
77	H	OH	14
78	OH	OH	17
79	OH	OH	14
80	H	H	14

The 5,6-Dihydropyrimidine nucleosides have attracted attention as potential antiviral and antitumor agents.[224,225] Physiological dihydro nucleosides play an important role in nucleic acid metabolism and appear frequently in the sequence of tRNA.[226] 5,6-

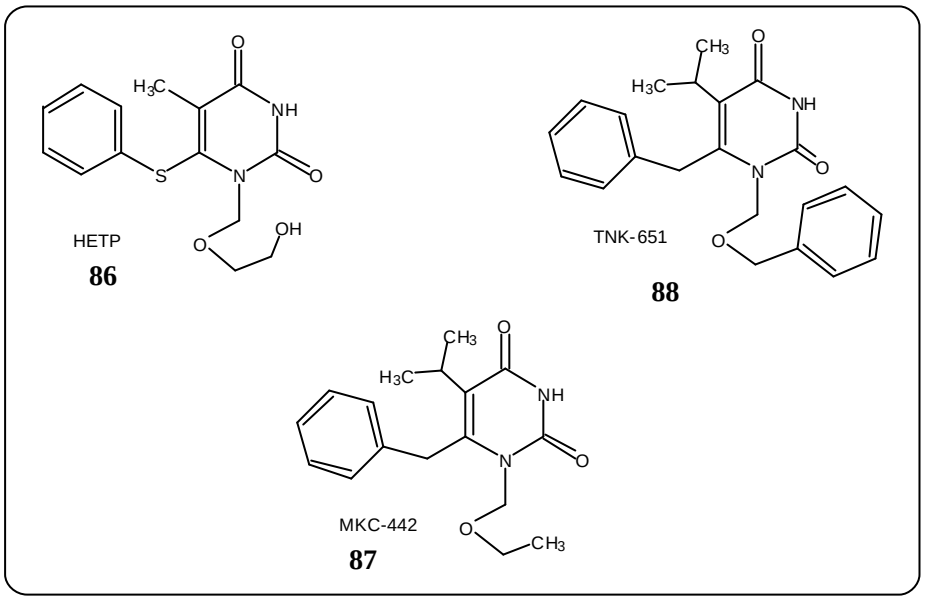
dihydro analogues of thymidine **(81c)** can act as competitive substrates, to thymidine, for thymidine kinase.[227,228] 5-Fluoro-6-hydroxy (or acetoxy)-5,6-dihydro-2'-deoxyuridine diastereomers **(81a,b)** have been investigated as prodrugs to 5-fluoro-2'-deoxyuridine.[224] The 5,6-dihydro derivatives **(81d–f)** of antiviral pyrimidine nucleosides as potential prodrugs.[229-234] It was observed that the groups at C-5 and C-6 positions in the 5,6-dihydro derivatives created a potentially interesting enhancement of lipophilicity with respect to that of the parent nucleosides. It was also found that 5,6-dihydropyrimidine nucleosides **(81d–f)** serve as slow releasers (prodrugs) of the parent nucleosides *in vivo* and were stable to glycosidic bond cleavage. These beneficial properties of 5,6-dihydropyrimidine nucleosides **(81d–f)** encouraged us to further investigate 5,6-dihydro derivatives of 2'-deoxyuridine and -thymidine to study their biological activity.

Rakesh Kumar[235] synthesized, antiviral and cytotoxic activities of 5-bromo (or chloro)-6-azido-5,6-dihydro-20-deoxyuridine **(82,83)** and thymidine **(84,85)**. Compounds exhibited a broad spectrum of antiherpes activity against (HSV-1, HSV-2, HCMV, and VZV).

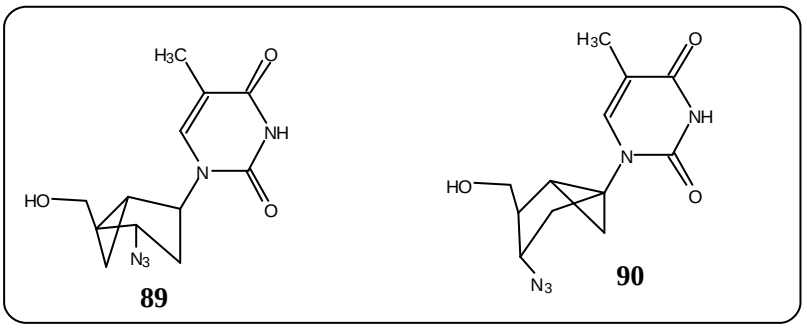


Andrew L. H. et al.[236] studied compounds belong to the HEPT **(86)** chemical series.[237-241] HEPT, or 1-[(2-hydroxyethoxy)-methyl]-6-(phenylthio)thymine, was one of the earliest NNIs discovered but inhibits HIV-1 RT relatively weakly (IC50) 17 μM).[237-242] MKC-442 **(87)**, or 6-benzyl-1-(ethoxymethyl)- 5-isopropyluracil (I-EBU), is a very potent inhibitor of HIV-1 RT (the IC_{50} being 2000-fold lower at 8 nM),[243,244] although only three relatively minor alterations have been made to the HEPT structure.

The different spectrum of drug-resistance mutations between HEPT and MKC-442 parallels the variation in potency. A single mutation (Tyr188His) renders the virus effectively resistant to HEPT.[245]

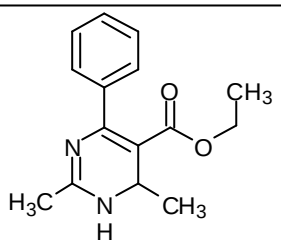


Victor E. M.et al.[246] synthesized 5'-triphosphates of(**89)** and **(90)** were evaluated directly as reverse transcriptase(RT) inhibitors using both a recombinant enzyme and enzyme obtained and purified directly from wild-type viruses. The results showed that inhibition of RT occurred only with the conformationally locked$_2$*E* (N)-*methano*-carba-AZT 5'-triphosphate. This inhibition was equipotent to and kinetically indistinguishable from that produced by AZT 5'-triphosphate. The antipodal $_3$*E* (S)-*methano*-carba-AZT 5'-triphosphate, on the other hand, did not inhibit RT.



New drug molecules under clinical study:

Recently many new molecules which are under study from phase-I to Phase-IV clinical trials for different pharmacological action have shown that the basic characteristic of morpholine to behave as hidden amine has attracted many medicinal chemists to incorporate this feature in drug design. Some interesting compounds are as under.



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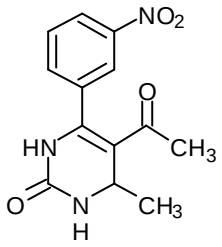
Treatment of Hypertension

Calcium Channel Blokers



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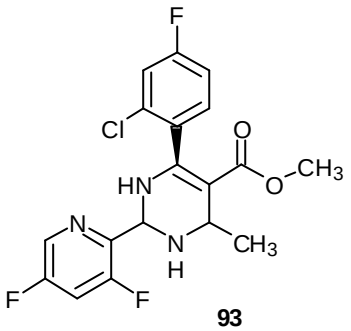
Calcium Channel Blokers[247]

Company Name: Merck & Co.

Moreover one compounds[248] is very active against Non-nucleoside inhibitor of human hepatitis B virus (IC50 = 53 nM for reduction of HBV DNA in human hepatoma HepG2.2.15 cells) with low cytotoxicity in uninfected cells (CC50 = 7 mcM). Compound inhibited both viral DNA and viral cores in HepG2.2.15 cells and HBV-transfected cell lines, whereas it did not affect the activity of endopolymerase and had no effect on other DNA or RNA viruses. *In vivo* in a transgenic mouse model, oral doses of 3-100 mg/kg b.i.d. or t.i.d. for up to 28 days dose-dependently.

decreased viral DNA in the liver and plasma with efficacy comparable to lamivudine. However, unlike lamivudine, compound reduced cytoplasmic HBV core antigen (HBcAg) in the liver of mice. Pharmacokinetic studies in mice showed rapid absorption, 30% bioavailability and dose-proportional plasma levels.

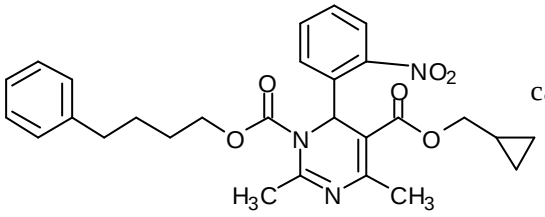


93

Name : Bay-41-4109

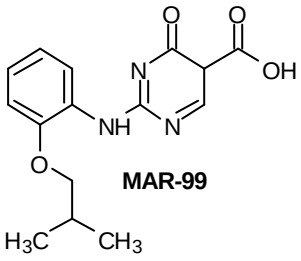
Anti Hepatitis B Virus Drugs[249]

Bayer



94

calcium channel blocker[250]



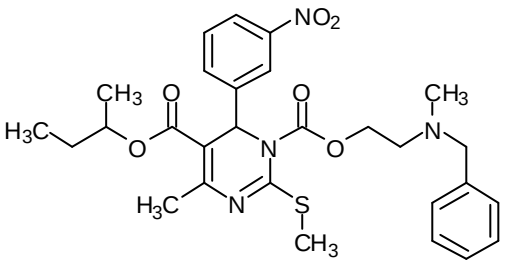
MAR-99

95

MAR-99

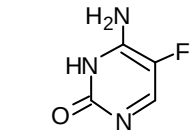
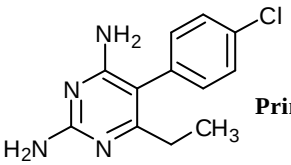
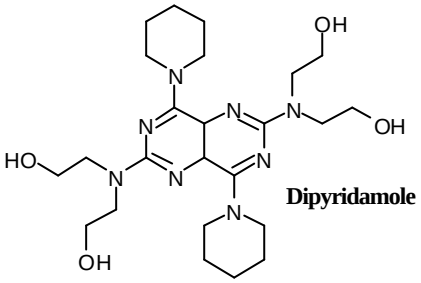
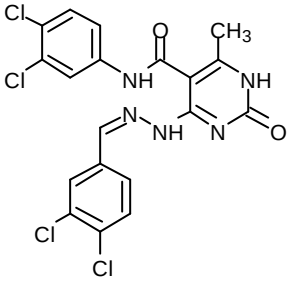
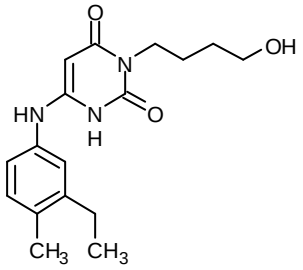
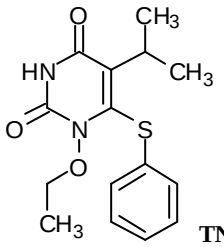
Leukotrine Antagonist[251]

(Known anti-asthmatic agent, now reported to possess anti-ulcerative and gastric antisecretory activities, which inhibits hydrochloric acid-ethanol-, stress- and indomethacin-induced ulcers in rat.



96

Calcium Channel Blockers[252]

 **Flucytosine** (fluorocytosine)	Antifungal Agent.[253] *In vitro* susceptibility of Candida species isolated from cancer patients against some antifungal agents.
 **Primethamine**	Antimalarial Agent.[254]
 **Dipyridamole**	Acute Myocardial Infection Treatment of Antiplatlet Therapy.
	Immunosuppressants Oncolytic Drug
	Antibacterial Drugs 39th Intersci Conf Antimicrob Agents Chemother (Sept 26-29, San Francisco) 1999, Abst F1808 *In vitro* activity of novel 6-anilinouracils targeted to DNA polymerase III of Gram-positive bacteria
 **TNK-6123**	**TNK-6123** Anti HIV Agent Reverse Transcripase Inhibitors. **Non-nucleoside HIV-1 reverse transcriptase inhibitor Compound was active not only against wild-type HIV-1 strains (IC50 = 3 nM against IIIB and NL4-3 HIV-1 strains) but also showed nanomolar**

With an intention of preparing the compounds possessing better therapeutic activity, we have undertaken the synthesis of dihydropyrimidinones which have been described in following sections

SECTION-I **SYNTHESIS AND BIOLOGICAL SCREENING OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDRO PYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES**

SECTION-II **SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDRO PYRIMIDIN-2(1H)-ONE-5-CARBOXYLATES.**

SECTION-III **SYNTHESIS AND BIOLOGICAL SCREENING OF N-(2,4-DI CHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES.**

SECTION-IV **SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES.**

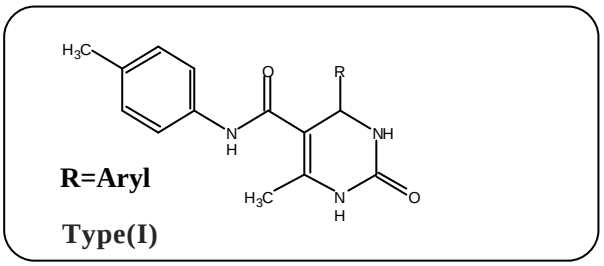
SECTION-V **SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXAMIDES.**

SECTION-VI **SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXY PHE NYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES.**

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES.

Much interest have been focused around dihydropyrimidinone derivatives because of their wide variety of pharmacologidal properties and industrial applications. In view of these findings and achieve to better drug potency, we have synthesized 6-Methyl-N-(4-methylphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxamides of Type (I) by the condensation of N-(4-methylphenyl)-3-oxobutanamide with urea and aryl aldehydes.



R=Aryl

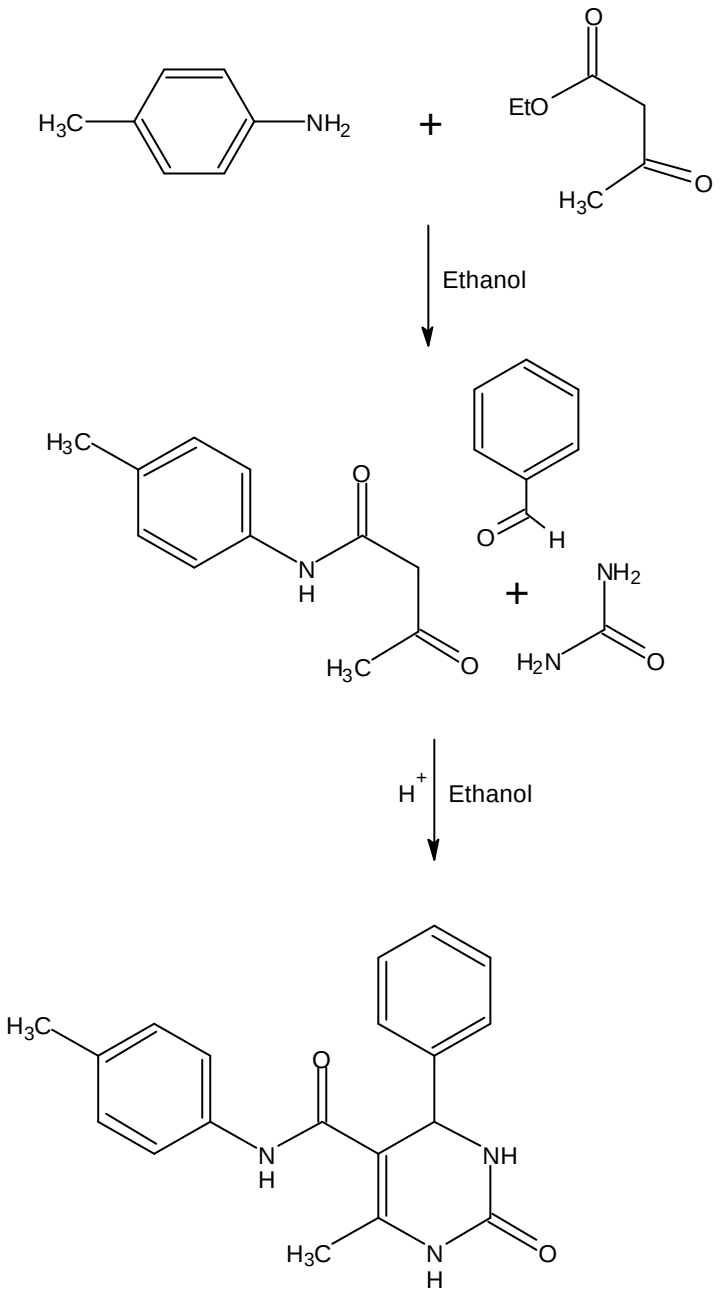
Type(I)

The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards *Aspergillus niger* at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Moreover, some selected compounds have been evaluated for their ***in vitro*** biological assay towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at a concentration of 6.25 µg/ml using Rifampin as a standard drug which have been tested at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF), Alabama, U. S. A.

Reaction Scheme



ANTIMICROBIAL ACTIVITY

Method	:	Cup-Plate[257]
Gram positive bacteria	:	***Bacillus cocus***
		Bacillus subtillis
Gram negative bacteria	:	***Proteus Vulgaris***
		Escherichia Coli
Fungi	:	***Aspergillus niger***
Concentration	:	40µg/ml
Solvent	:	Dimethyl formamide
Standard drugs	:	Amoxicillin, Ampicillin, Benzyl penicillin, Norfloxacin, Greseofulvin

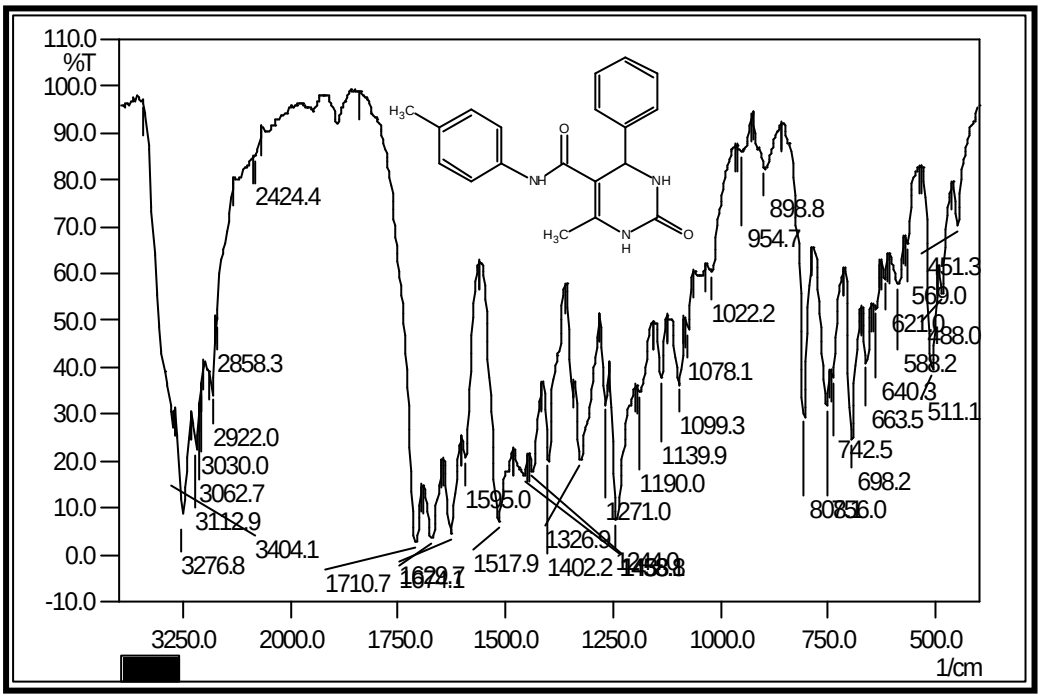
The antimicrobial activity was compared with standard drug viz Amoxicillin, Ampicillin, Benzyl penicillin, Norfloxacin, Greseofulvin and antifungal activity was compared with viz Greseofulvin. The inhibition zones measured in mm.

ANTITUBERCULAR ACTIVITY

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF) U.S.A.

Method	:	BACTEC 460 Radiometric system.
Bacteria	:	Mycobacterium Tuberculosis $H_{37}Rv$
Concentration	:	6.25 µg/ml.
Standard drug	:	Rifampin.

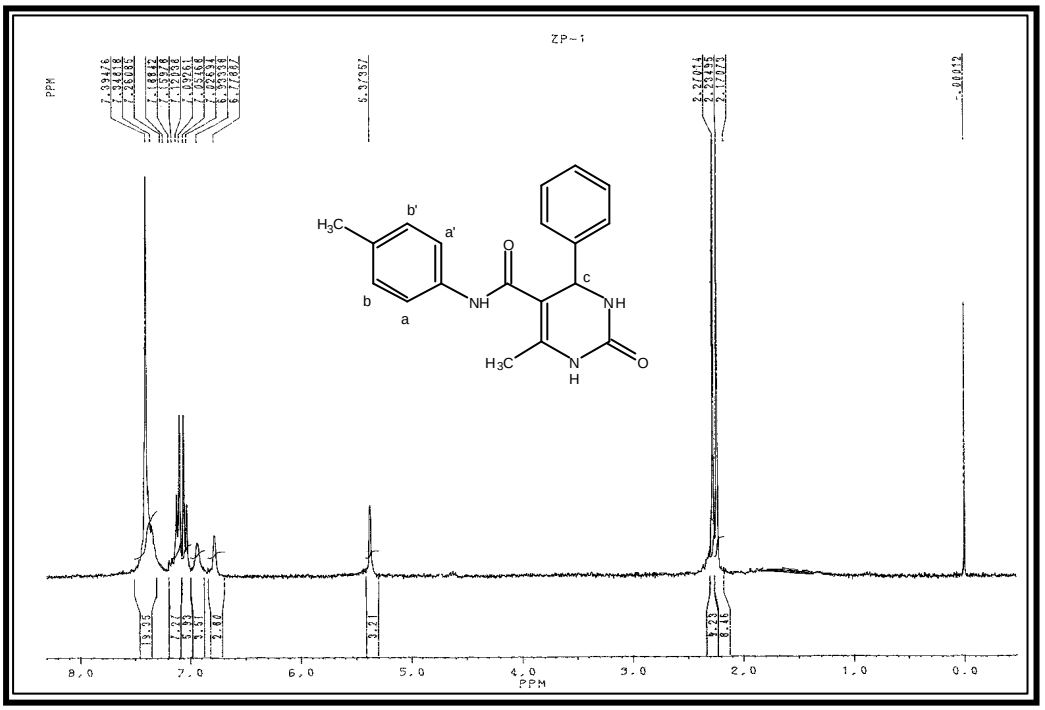
IR SPECTRAL STUDIES OF 6-METHYL-N-(4-METHYLPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDE.



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2922	2975-2950	255
-CH_3	C-H str. (sym.)	2858	2880-2860	,,
	C-H i.p.def. (asym.)	1458	1470-1435	,,
	C-H o.o.p. def. (sym.)	1327	1390-1370	,,
Aromatic	C-H str.	3030	3090-3030	256
	C=C str.	1498	1540-1480	,,
		1402	1520-1480	,,
	C-H i.p. (def.)	1078	1125-1090	,,
	C-H o.o.p. (def)	808	835-810	,,
Pyrimidine	C=C str.	1595	1580-1520	,,
moity	C-H str.	3062	3080-3030	,,
	C-H i.p. def.	1099	1125-1090	,,
Amine	-NH str.	3404	3410-3380	255
	-NH def.	1629	1635-1595	,,
Cabonyl	-C=O str.	1710	1700-1725	,,
Amide	- C=O str.	1674	1690-1660	,,

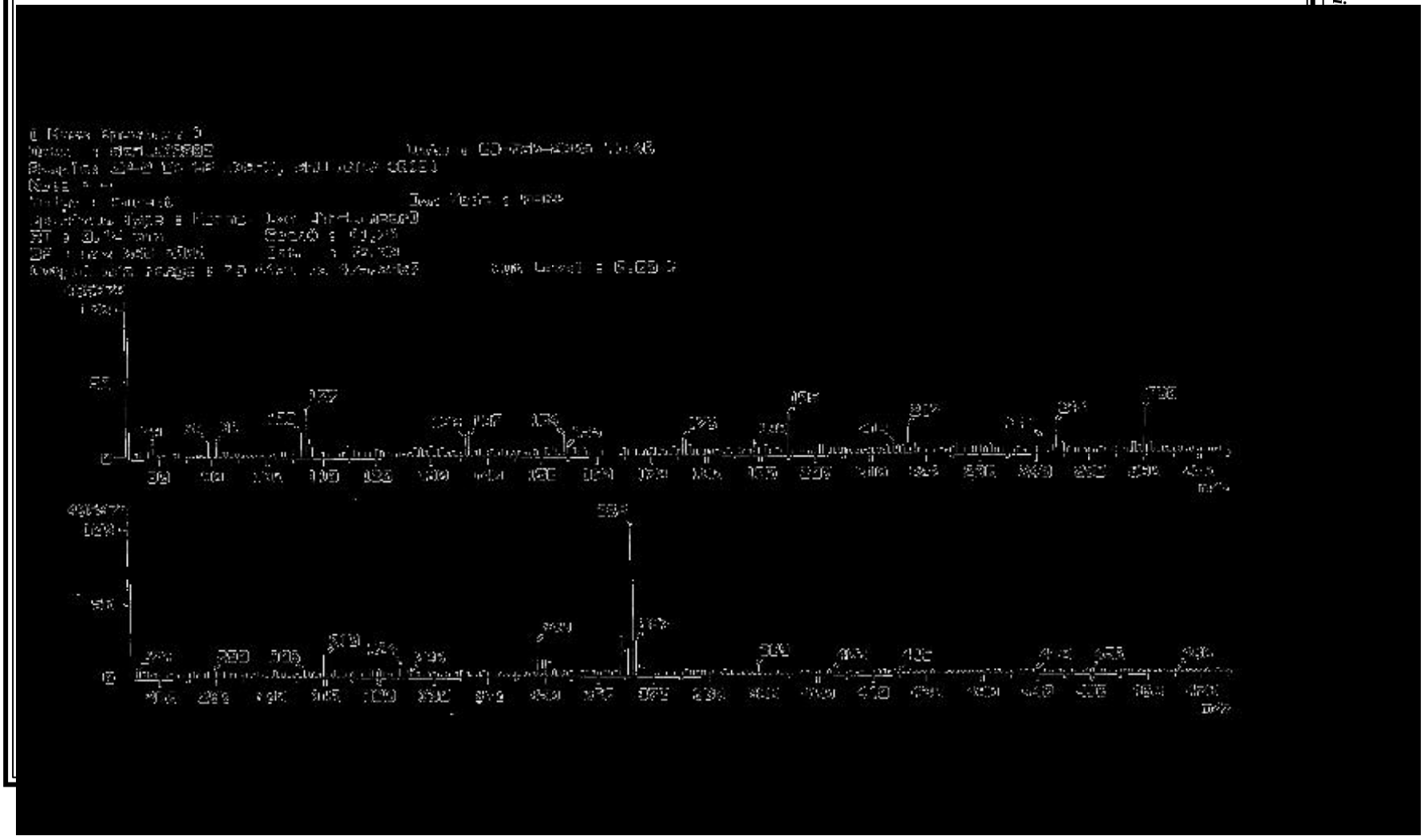
NMR SPECTRAL STUDIES OF 6-METHYL-N-(4-METHYLPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.17	3H	singlet	-CH_3(Pyr.)	-
2	2.23	3H	singlet	Ar-CH_3	-
3	5.37	1H	singlet	Ar-Hc	-
4	7.02-7.05	2H	doublet	Ar-Ha,a'	Jaa'=9.0
5	7.09-7.19	2H	doublet	Ar-Hb,b'	Jbb'=9.0
6	7.39	5H	multiplate	Ar-H	-
7	6.77	1H	singlet	-NH(Amide)	
8	6.93	1H	singlet	-NH(Pyr.)	-

MASS SPECTRAL STUDIES OF 6-METHYL-N-(4-METHYLPHENYL)-4-(3-NITROPHENYL)-3,4-DIHYDROPYRIMIDIN-



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES.

(A) Synthesis of N-(4-methylphenyl)-3-oxobutanamide.

A mixture of ethyl acetoacetate (1.30 gm, 0.01 mol) and p-toluidine (1.07gm, 0.01 mol) in ethanol was refluxed for 12 hrs. The resulting solution was poured on to crushed ice. The separated solid was filtered and crystallized from ethanol, Yield 74%, m. p. 192^{0}C, Anal.Calcd. for $C_{11}H_{13}NO_2$ Calcd: C, 69.09; H, 6.85; N, 7.32%, Found: C, 69.07; H, 6.84; N, 7.30%.

(B) Synthesis of 6-Methyl-N-(4-methylphenyl)-4-phenyl-3,4-dihydro pyrimidin-2(1H)-one-5-carboxamide.

A mixture of urea (0.60 gm, 0.01 mol), benzaldehyde (1.06 gm, 0.01 mol) and N-(4-methyl phenyl)-3-oxobutanmide (1.91 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^{0}C. The resulting solid mass separated was filtered and, crystallized from dioxane. Yield 34%, m. p. 250^{0}C, Anal.Calcd. for $C_{19}H_{19}N_3O_2$ Calcd: C, 71.01; H, 5.96; N, 13.08%, Found: C, 69.99; H, 5.94; N, 13.06%.

Similarly, other 6-Methyl-N-(4-methylphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxamides were prepared. The physical data are recorded in Table No. 1

(C) Biological screening of 6-Methyl-N-(4-methylphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxamides.

(a) Antibacterial activity[257]

The purified products were screened for their antibacterial activity using cup-plate agar diffusion method. The nutrient agar broth prepared by the usual method was inoculated aseptically with 0.5 ml of 24 hrs. old subcultures of Bacillus cocus, Bacillus subtillis, Proteus Vulgaris and Escherichia Coli in separate conical flasks at 40-50 ^{0}C and mixed well by gentle shaking. About 25 ml content of the flask was poured and evenly spreaded in a petridish (13 cm diameter) and allowed to set for 2 hrs. The cups (10 mm diameter) were formed by the help of borer in agar medium and filled with 0.04ml (40mg) solution of sample in DMF.The plates were incubated at 37 ^{0}C for 24 hrs. and the control was also maintained with 0.04ml of DMF in a similar manner and the zone of inhibition of the bacterial growth were measured in millimeter and recorded in Graphical Chart No. 1

(b) Antifungal activity[257]

A. niger was employed for testing antifungal activity using cup-plate agardiffusion method. The culture was maintained on sabourauds agar slants sterilized sabourauds agar medium was inoculated with 72 hrs. old 0.5ml suspension of fungal spores in a separate flask. About 25ml of the inoculated medium was evenly spreaded in a petridish (13cm diameter) and allowed to set for 2 hrs. the cups (10mm diameter) were punched. The plates were incubated at 30 ^{0}C for 48 hrs. After the completion of incubation period, the zone of inhibition of growth in the form of diameter in mm was measure. Along the test solution in each petridish one cup was filled up with solvent, which acts as control. The zone of inhibition of test solution are recorded in Graphical Chart No. 1

(C)Antitubercular activity

The antitubercular evaluation of the compounds was carried out at Tuberculosis Antimicrobial Acquisition and Co-ordination Facility (TAACF), USA.

Primary screening of the compounds for the antitubercular activity have been conducted at 6.25 mg/ml towards ***Mycobacterium tuberculosis $H_{37}Rv$*** in BACTEC 12B using the BACTEC 460 radiometric system. The compounds demonstrating atleast>90% inhibition in the primary screening has been tested at lower concentration towards ***Mycobacterium tuberculosis $H_{37}Rv$*** to determine the actual minimum inhibitory concentration (MIC) in the BACTEC-460.

The antitubercular data have been compared with standard drug Rifampin at 6.25 mg/ml concentration and it showed 98% inhibition. The primary screening method is described as under.

Antitubercular activity was determined using the BACTEC 460 system as modified below. Stock solutions as test compounds were prepared in dimethylsulfoxidie (DMSO) at 1 mg/ml and sterilized by passage through 0.22 mm PFTE filters (Millex-FG, Millipore, Bedford MA). Fifty microliters was added to 4ml radiometric 7H12 broth (BACTEC 12B; Becton Dickinson Diagnostic Instrument System, Sparks, MD) to achieve a final concentration of 6.25 mg/ml. Controls received 50 ml DMSO. Rifampin was solublized and diluted in DMSO And added to bactec-12 broth to achieve a range of concentration for determination of minimum inhibitory (MIC, lowest concentration inhibiting 99% of the inoculum).

M. Tuberculosis $H_{37}Rv$ (ATCC 27294; American type culture collection, Rockville, MD) was culture at 37 ^{0}C on a rotary shaker in middlebrook 7H9 broth (Difco Laboratories, Detroiet, MI) supplemented with 0.2 v/v glycerol and 0.05% v/v Tween 80 until the culture turbidity achieved an optical density of 0.45-0.55 at 550nm. Bacteria were then pelleted by centrifugation, washed twice and resuspended in one fifth the original volume in dulbecco's phosephate buffered saline (PBS, Irvine Scientific Santa, Nalgene, Rochester, NY) and aliquots were frozen at 80 ^{0}C. Cultures were showed and an appropriate dilution performed such that a BACTEC-12B vial inoculated with a 0.1 ml would reach a growth index (GI) of 999 in 5 days.

One tenth of diluted inoculum was used to inoculate 4 ml fresh BACTEC 12B broth containing the compounds. An additional control vial was included which received a further 1;100 diluted inoculam (as well as 50 ml DMSO) use an calculating the MIC of Rifampin, respectively by establishing procedures.

Cultures were incubated in 37 ^{0}C and the GI determined daily until control cultures achieved a GI og 999. Assays were usually completed in 5-8days. Percent inhibition was defined as-1- (GI of test sample/GI of control) x 100. Minimum inhibitory concentration of compound effecting a reduction in daily chang in GI, which was less than that, observed with a 1:100 diluted control culture one day the letter reached a GI of at least 30. The percentage of inhibition data of compounds are recorded in Table No. 1

TABLE-1 : PHYSICAL CONSTANTS OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H) -ONE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
1a	C_6H_5-	$C_{19}H_{19}N_3O_2$	321	250	34	13.08	13.06	0.51	S1
1b	2-Cl-C_6H_4-	$C_{19}H_{18}ClN_3O_2$	356	170	46	11.81	11.80	0.42	S2
1c	3-Cl-C_6H_4-	$C_{19}H_{18}ClN_3O_2$	356	271	48	11.81	11.79	0.55	S1
1d	4-F-C_6H_4-	$C_{19}H_{18}FN_3O_2$	339	252	44	12.38	12.36	0.44	S1
1e	2-NO_2-C_6H_4-	$C_{19}H_{18}N_4O_4$	366	289	38	15.29	15.28	0.59	S2
1f	3-NO_2-C_6H_4-	$C_{19}H_{18}N_4O_4$	366	210	49	15.29	15.27	0.54	S2
1g	4-OCH_3-C_6H_4-	$C_{20}H_{21}N_3O_3$	351	221	45	11.96	11.94	0.41	S2
1h	2-OH-C_6H_4-	$C_{19}H_{19}N_3O_3$	337	280	48	12.46	12..45	0.56	S2
1i	4-OH-C_6H_4-	$C_{19}H_{19}N_3O_3$	337	310	41	12.46	12.44	0.44	S1
1j	2,5-$(OCH_3)_2$ -C_6H_3-	$C_{21}H_{23}N_3O_4$	381	301	32	11.02	11.00	0.47	S1
1k	3-C_6H_5-O-C_6H_4-	$C_{25}H_{23}N_3O_3$	413	321	51	10.16	10.15	0.53	S2
1l	$C_{10}H_7$-	$C_{23}H_{21}N_3O_2$	371	223	56	11.31	11.28	0.45	S2

S1 Hexane:Ethyl acetate(7:3), S2 Hexane:Ethyl acetate(6:4)

ANTITUBERCULAR ACTIVITY OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES.

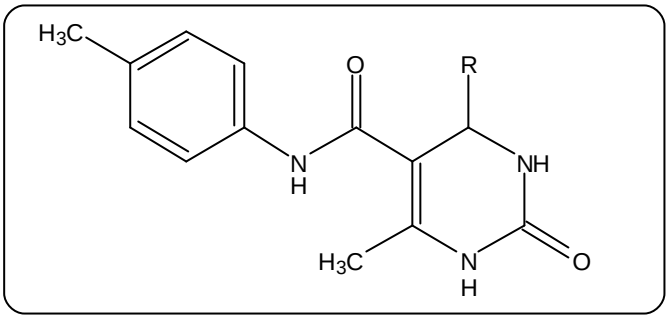


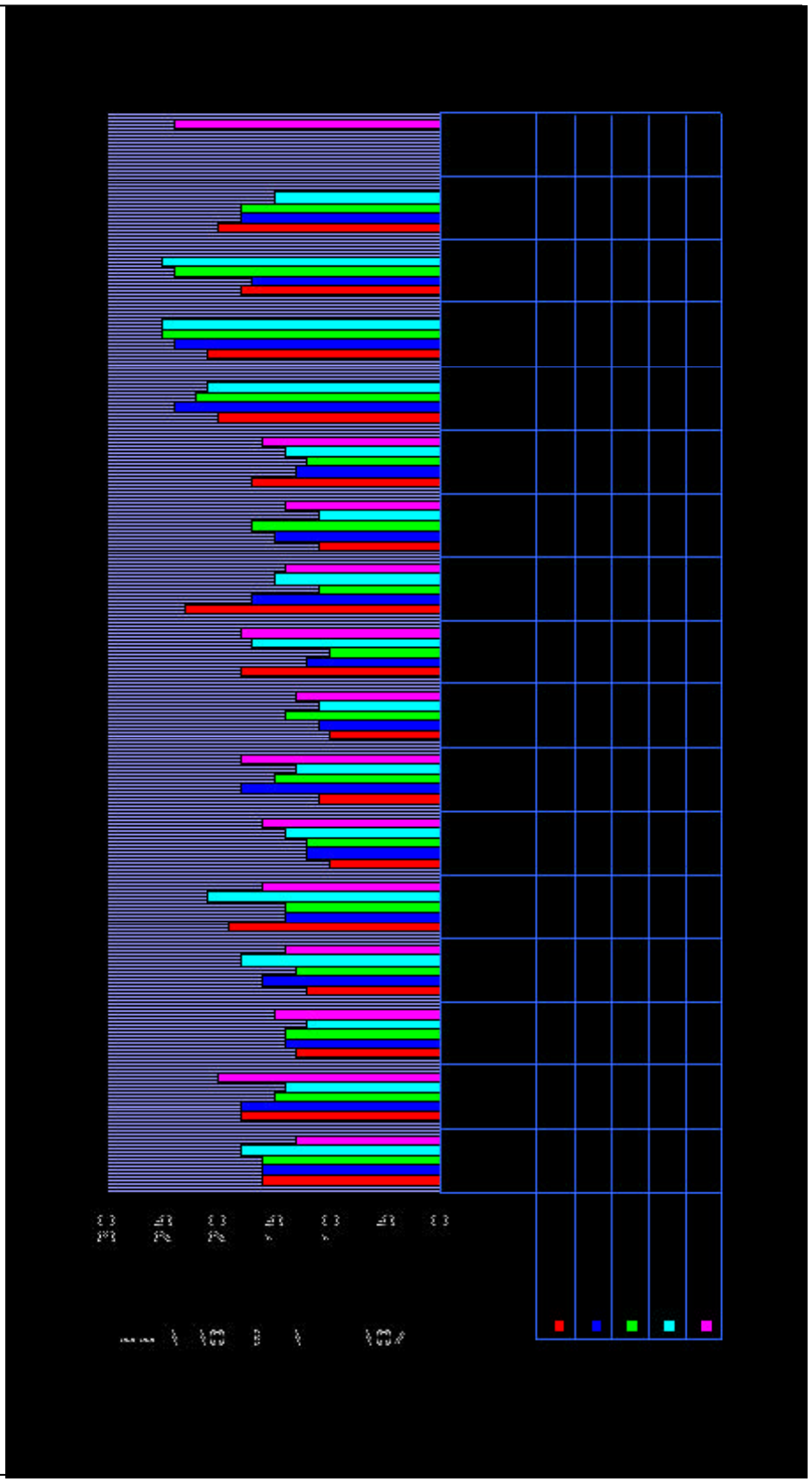
TABLE NO-1

TAACF, Southern Research Insitute

Primary Assay Summary Report

Sr. No.	Sample ID	Corp ID	R	Assay	Mtb Strain	MIC mg/ml	% Inhibi.
1a	179637	ZP-1	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	00
1b	179638	ZP-2	2-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
1c	179639	ZP-3	3-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	20
1d	179640	ZP-4	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
1e	179641	ZP-5	2-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	65
1f	179642	ZP-6	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
1g	179643	ZP-7	$C_{10}H_7$-	Alamar	$H_{37}Rv$	>6.25	24
1h	179644	ZP-8	3-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	11
1i	179645	ZP-9	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	24
1j	179646	ZP-10	2,5-$(OCH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	07
1k	179647	ZP-11	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	13
1l	179648	ZP-12	3-C_6H_5O-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	32

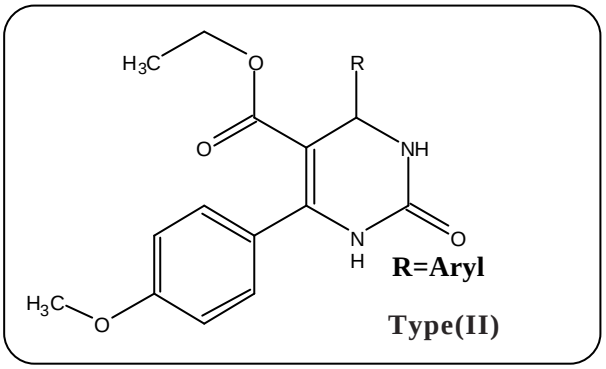
GRAPHICAL CHART NO. 1 : ANTIMICROBIAL ACTIVITY OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES



SECTION - II

SYNTHSIS AND BIOLOGICAL SCREENING OF ETHYL-6-(4-METHOXY PHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXYLATES.

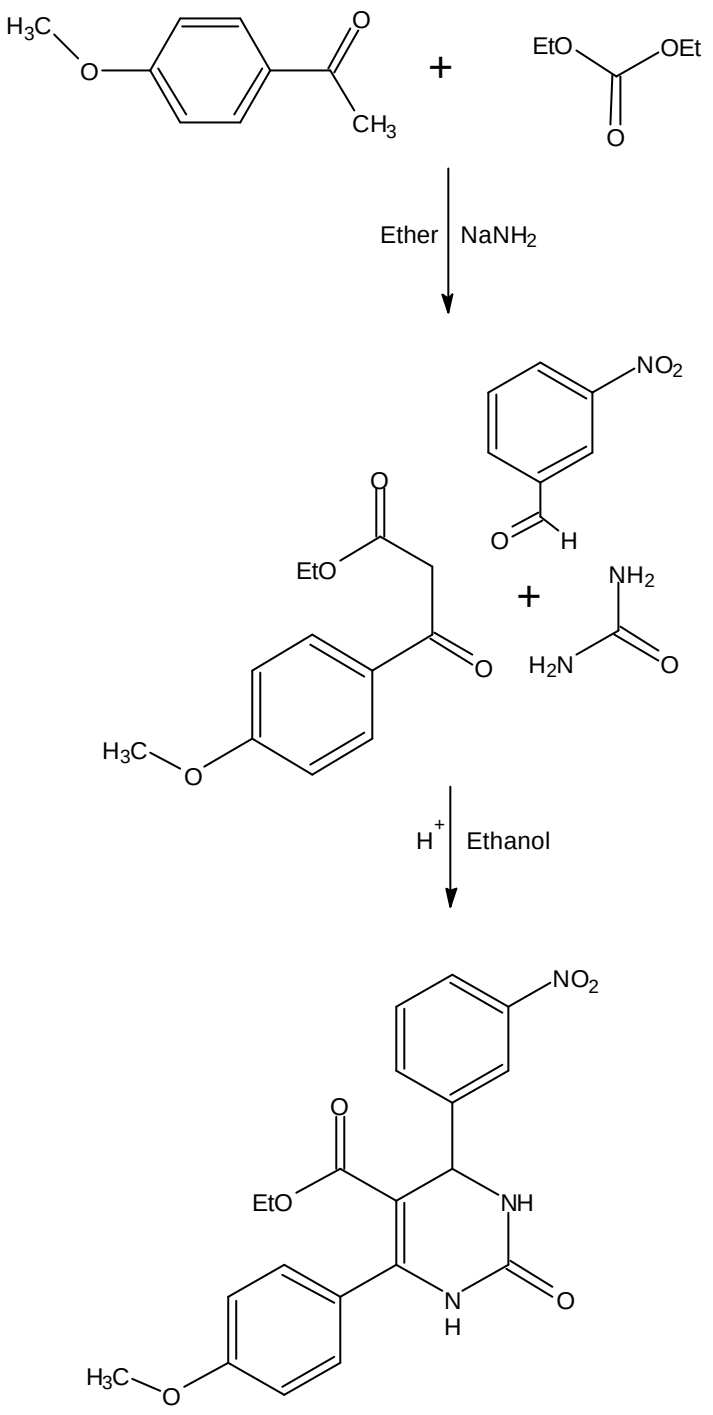
Compounds containing pyrimidine ring are widely distributed in nature. Many of these derivatives are reported to possess different biological activities. In view of these reports, we have synthesized Ethyl-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxylates of Type (II) by the condensation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate,urea and aryl aldehydes.



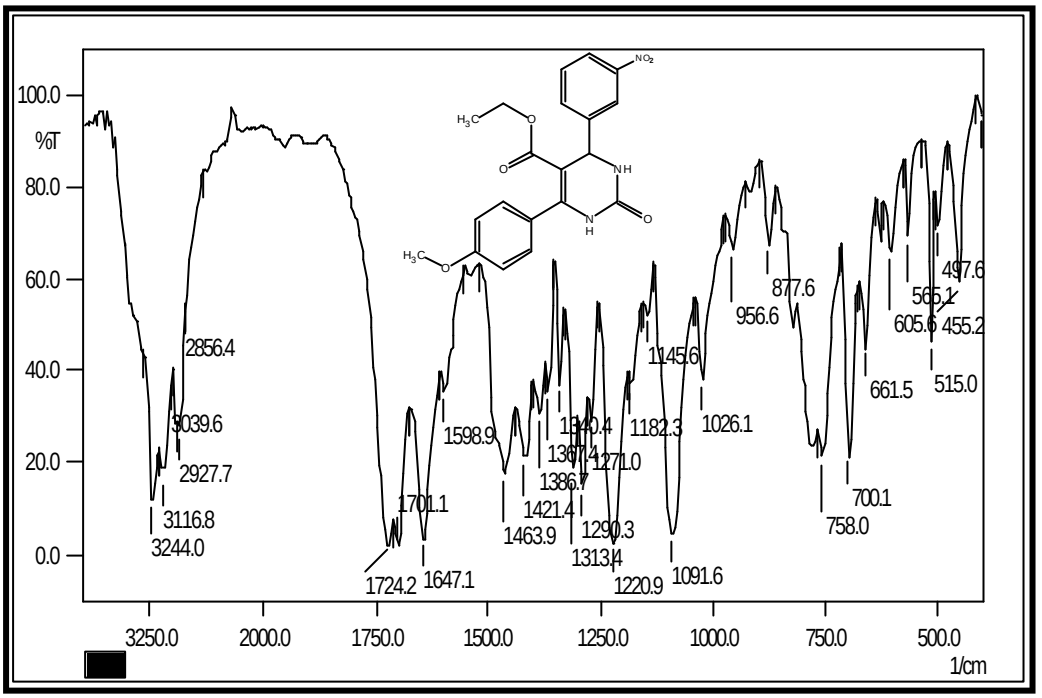
The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Reaction Scheme



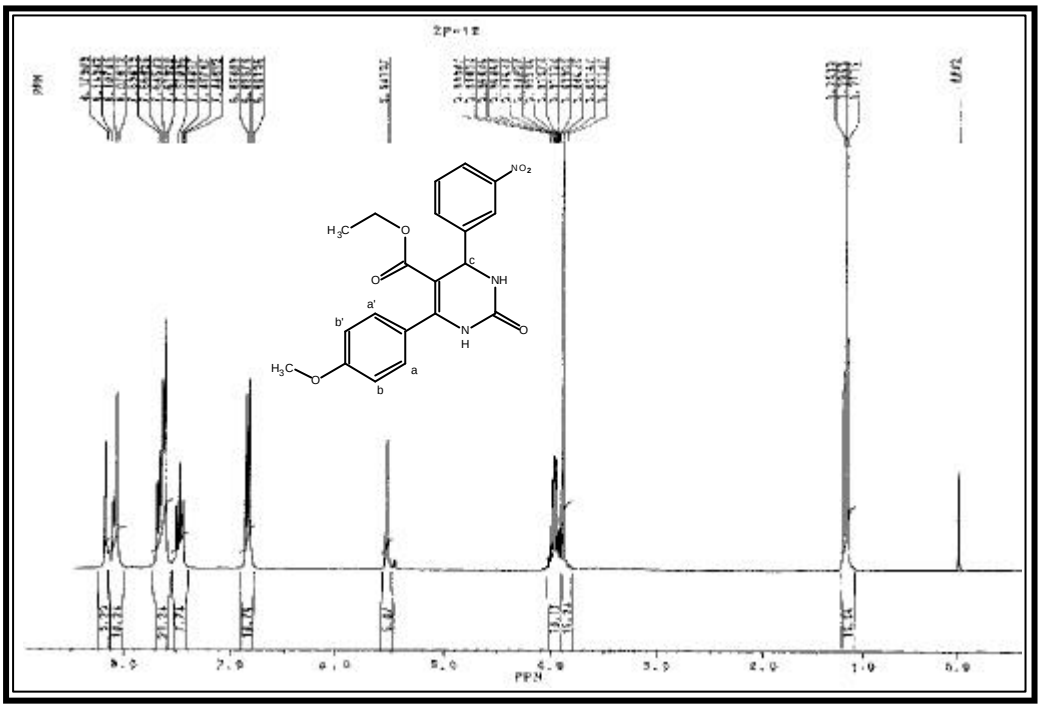
IR SPECTRAL STUDIES OF ETHYL-6-(4-METHOXYPHENYL)-4-(3-NITROPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-CARBOXYLATE.



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2927	2975-2950	255
$-CH_3$	C-H str. (sym.)	2856	2880-2860	,,
	C-H i.p.def. (asym.)	1463	1470-1435	,,
	C-H o.o.p. def. (sym.)	1340	1390-1370	,,
Aromatic	C-H str.	3116	3090-3030	256
	C=C str.	1464	1540-1480	,,
		1421	1520-1480	,,
	C-H i.p. (def.)	1091	1125-1090	,,
	C-H o.o.p. (def)	830	835-810	,,
Pyrimidine	C=C str.	1598	1580-1520	,,
moity	C-H str.	3039	3080-3030	,,
	C-H i.p. def.	1045	1125-1090	,,
Amine	-NH str.	3244	3410-3380	255
	-NH def.	1647	1635-1595	,,
Cabonyl	-C=O str.	1724	1700-1725	,,
Ester	- C=O str.	1701	1690-1660	,,

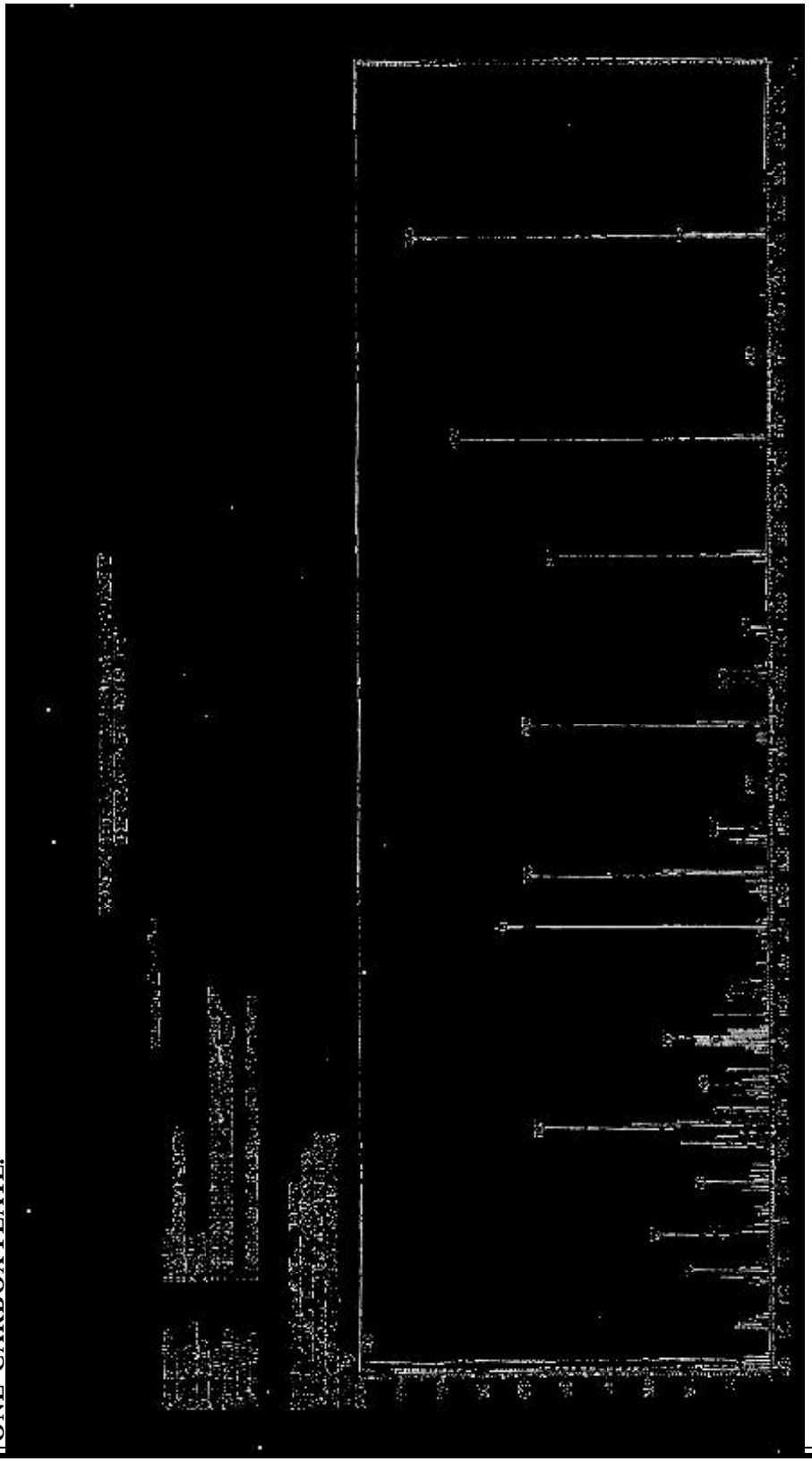
NMR SPECTRAL STUDIES OF ETHYL-6-(4-METHOXYPHENYL)-4-(3-NITROPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-CARBOXYLATE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.23	3H	triplet	$-CH_3$	-
2	3.86	3H	singlet	$Ar-OCH_3$	-
3	3.94	2H	quatret	$-CH_2$	-
4	5.54	1H	singlet	Ar-Hc	-
5	6.82-6.85	2H	doublet	Ar-Hb,b'	Jaa'=9.0
6	7.44-7.69	5H	multiplet	Ar-H	
7	8.07-8.10	2H	doublet	Ar-Ha,a'	Jbb'=9.0
8	8.14	1H	singlet	NH(Pyr.)	-

MASS SPECTRAL STUDIES OF ETHYL-6-(4-METHOXYPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-CARBOXYLATE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-6-(4-METHOXY PHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXYLATES.

(A) Synthesis of Ethyl-3-(4-methoxyphenyl)-3-oxopropanoate.

To a well stirred solution of liquid ammonia (30 ml), add minimum amount of sodium to produced a blue colour with few crystals of ferric nitrate. When all the sodium converted into sodium amide, p-metoxy acetophenone (15 gm, 0.1 mol) in 20 ml of diethyl ether was added over a period of five minutes. The reaction mixture was placed on a steam bath until all the ammonia evaporated. Then add diethyl carbonate (24.2 gm, 0.2 mol). The mixture was stirred and refluxed for 2 hrs. The resulting solution was poured over crushed ice and neutralize with glacial acetic acid. The ether phase was separated and was washed with sodium bicarbonate solution. Distilledd the ether and liquid was separated, Yield-85% b.p.190-192^{0}C, Anal.Calcd. for $C_{12}H_{14}O_4$ Calcd: C, 64.65; H, 6.35, Found: C, 6.62; H, 6.33,%.

(B) Synthesis of Ethyl-6-(4-methoxyphenyl)-4-(3-nitrophenyl)-3,4-dihydro pyrimidin-2(1H)-one-carboxylate.

A mixture of urea (0.60 gm, 0.01 mol), m-nitrobenzaldehyde (1.51 gm, 0.01 mol) and ethyl-3-(4-methoxyphenyl)-3-oxopropanoate (2.22 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^{0}C and the resulting solid mass separated was filtered and crystallized from dioxane.Yield 41%, m.p.301 ^{0}C, Anal.Calcd. for $C_{20}H_{19}N_3O_6$ Calcd: C,60.45; H, 4.82; N, 10.57%, Found: C, 60.43; H, 4.81; N, 10.54%.

Similarly, other Ethyl-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxylates were prepared. The physical data are recorded in Table No. 2

(C) Biological screening Ethyl-6-(4-methoxyphenyl)-4-aryl-3,4-dihydro-pyrimidin-2(1H)-one-5-carboxylates.

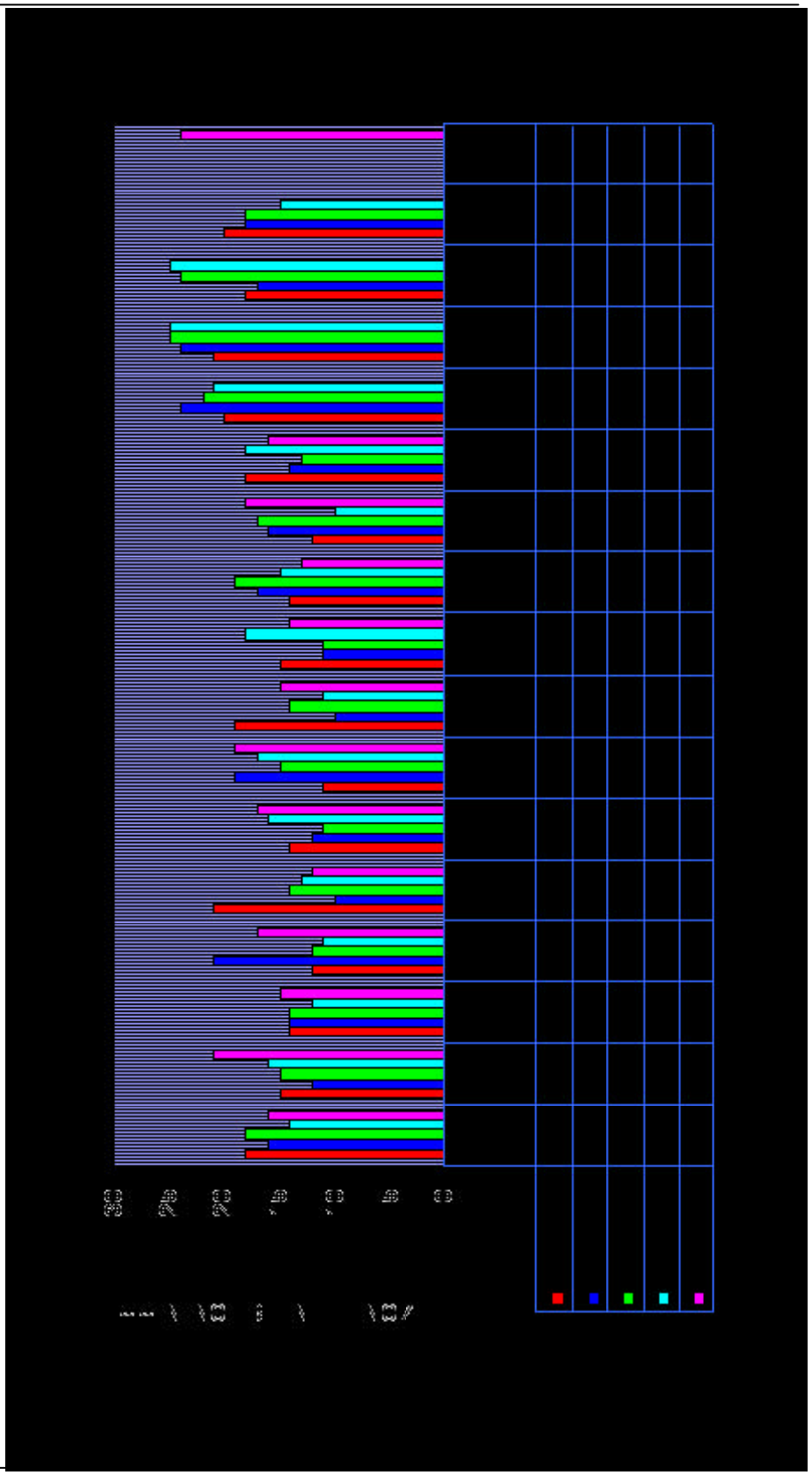
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.2

TABLE-2 :PHYSICAL CONSTANTS OF ETHYL-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXYLATES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
2a	C_6H_5-	$C_{20}H_{20}N_2O_4$	352	227	45	7.95	7.92	0.51	S1
2b	2-Cl-C_6H_4-	$C_{20}H_{19}ClN_2O_4$	387	212	36	7.24	7.22	0.45	S1
2c	3-Cl-C_6H_4-	$C_{20}H_{19}ClN_2O_4$	387	250	47	7.24	7.21	0.54	S2
2d	4-F-C_6H_4-	$C_{20}H_{19}FN_2O_4$	370	234	41	7.56	7.55	0.44	S1
2e	2-NO_2-C_6H_4-	$C_{20}H_{19}N_3O_6$	397	287	34	10.57	10.52	0.52	S2
2f	3-NO_2-C_6H_4-	$C_{20}H_{19}N_3O_6$	397	301	41	10.57	10.54	0.56	S1
2g	4-OCH_3-C_6H_4-	$C_{21}H_{22}N_2O_5$	382	298	48	7.33	7.32	0.31	S2
2h	4-OH-C_6H_4-	$C_{20}H_{20}N_2O_5$	368	245	47	7.60	7.69	0.53	S1
2i	2-OH,4-OCH_3-C_6H_3-	$C_{21}H_{22}N_2O_6$	398	285	35	7.03	7.02	0.49	S1
2j	2,5-$(OCH_3)_2$ -C_6H_3-	$C_{22}H_{24}N_2O_6$	412	247	39	6.79	6.75	0.41	S2
2k	3-C_6H_5-O-C_6H_4-	$C_{26}H_{24}N_2O_5$	444	312	37	6.30	6.26	0.50	S2
2l	$C_{10}H_7$-	$C_{24}H_{22}N_2O_4$	402	233	51	6.96	6.95	0.44	S2

S1 Hexane:Ethyl acetate(8:2), S2 Hexane:Ethyl acetate(5:5)

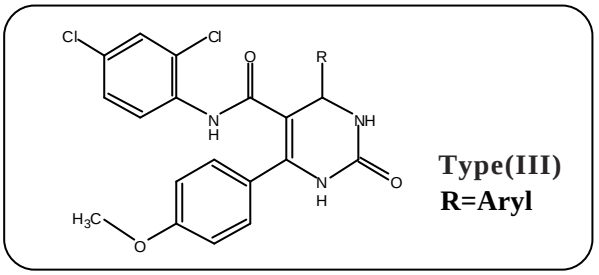
GRAPHICAL CHART NO. 2 : ANTIMICROBIAL ACTIVITY OF ETHYL-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXYLATES



SECTION - III

SYNTHESIS AND BIOLOGICAL SCREENING OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES.

Dihydropyrimidinone have been repported to have various pharmacological activities like antibacterial, antifungal, insecticidal etc. In order to achieving better drug potency, we have synthesized dihydropyrimidinone derivatives of type(III) by the cyclocondensation of N-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide,urea and aryl aldehydes.



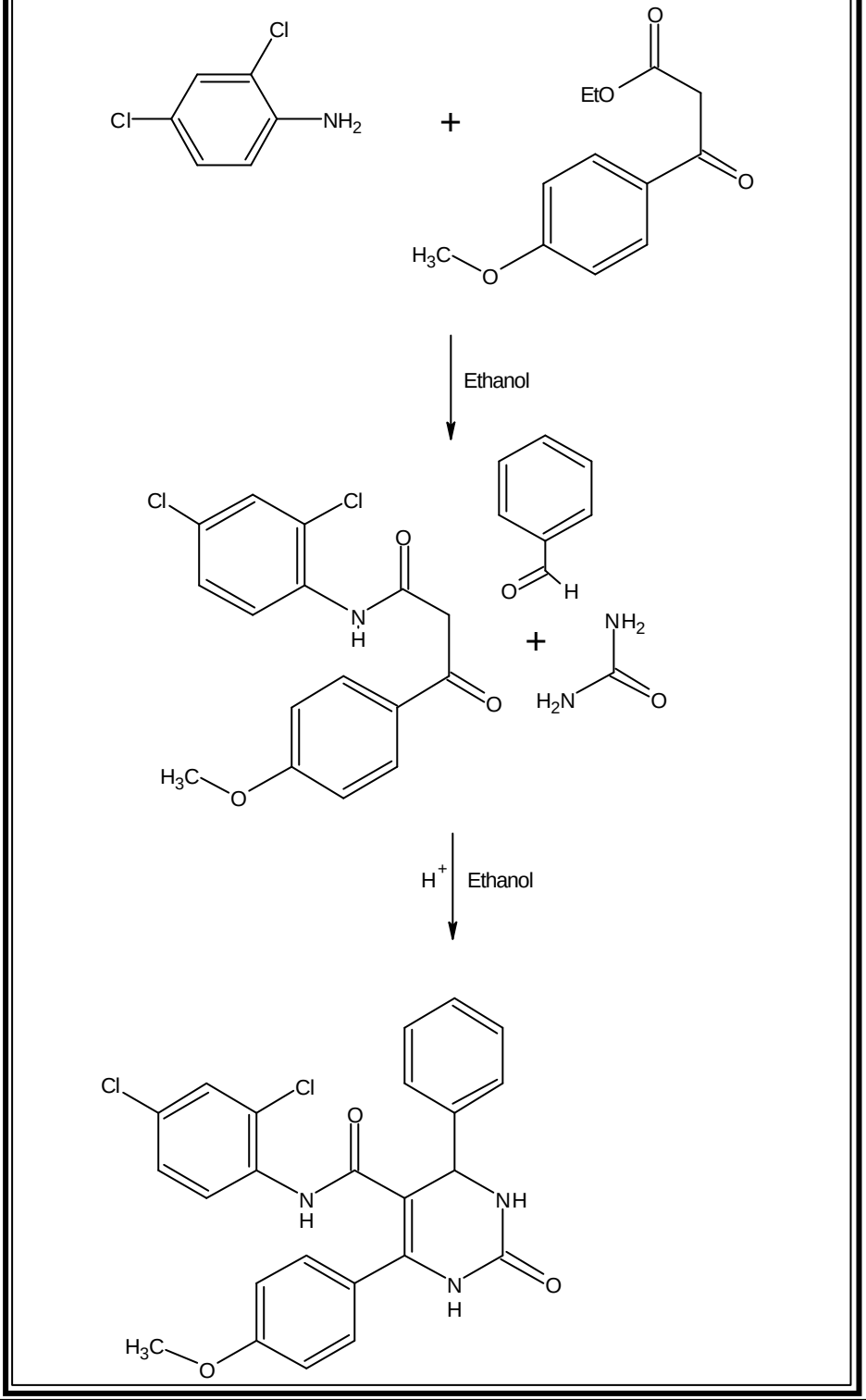
Type(III)
R=Aryl

The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

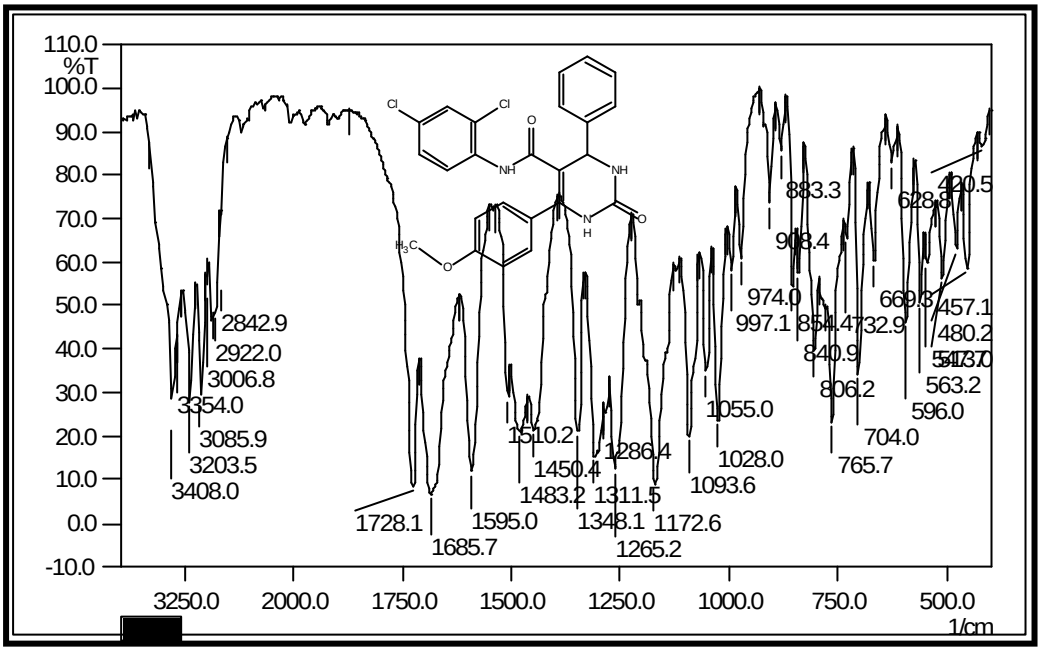
All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Moreover, some selected compounds have been evaluated for their ***in vitro*** biological assay towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at a concentration of 6.25 µg/ml using Rifampin as a standard drug which have been tested at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF), Alabama, U. S. A.

Reaction Scheme



IR SPECTRAL STUDIES OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDE.

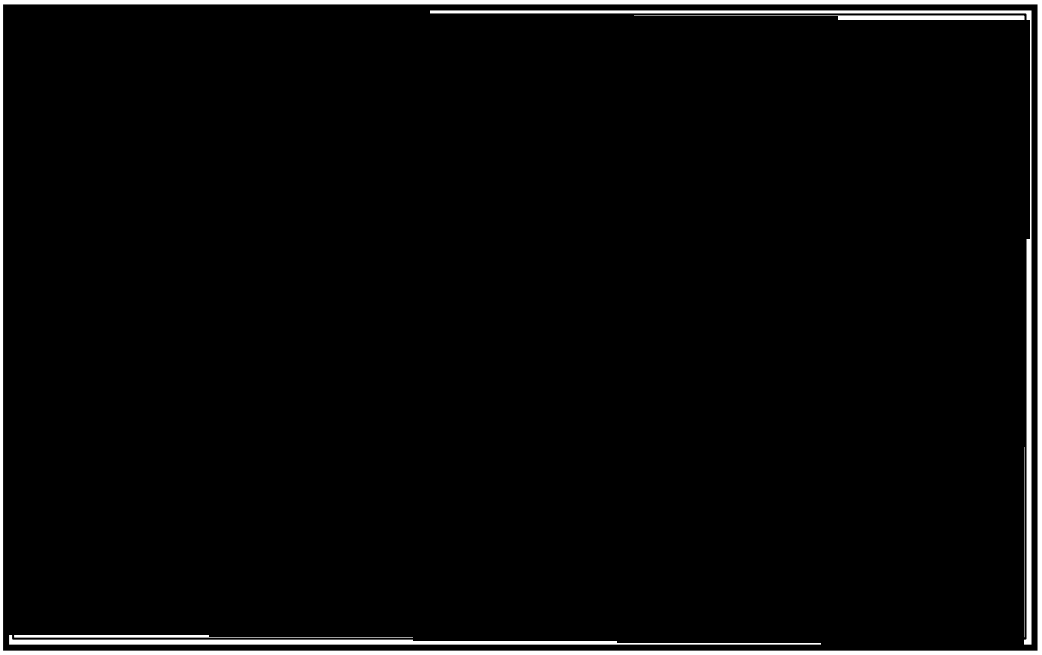


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range:4000-400 cm^{-1}

(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2922	2975-2950	255
-CH_3	C-H str. (sym.)	2842	2880-2860	,,
	C-H i.p.def. (asym.)	1450	1470-1435	,,
	C-H o.o.p. def. (sym.)	1348	1390-1370	,,
Aromatic	C-H str.	3086	3090-3030	256
	C=C str.	1483	1540-1480	,,
	C-H i.p. (def.)	1093	1125-1090	,,
	C-H o.o.p. (def)	806	835-810	,,
Pyrimidine	C=C str.	1510	1580-1520	,,
moity	C-H str.	3006	3080-3030	,,
	C-H i.p. def.	1055	1125-1090	,,
Amine	-NH str.	3408	3410-3380	255
	-NH def.	1595	1635-1595	,,
Cabonyl	-C=O str.	1728	1700-1725	,,
Amide	- C=O str.	1685	1690-1660	,,
Halide	-C-Cl str.	704	700-750	,,

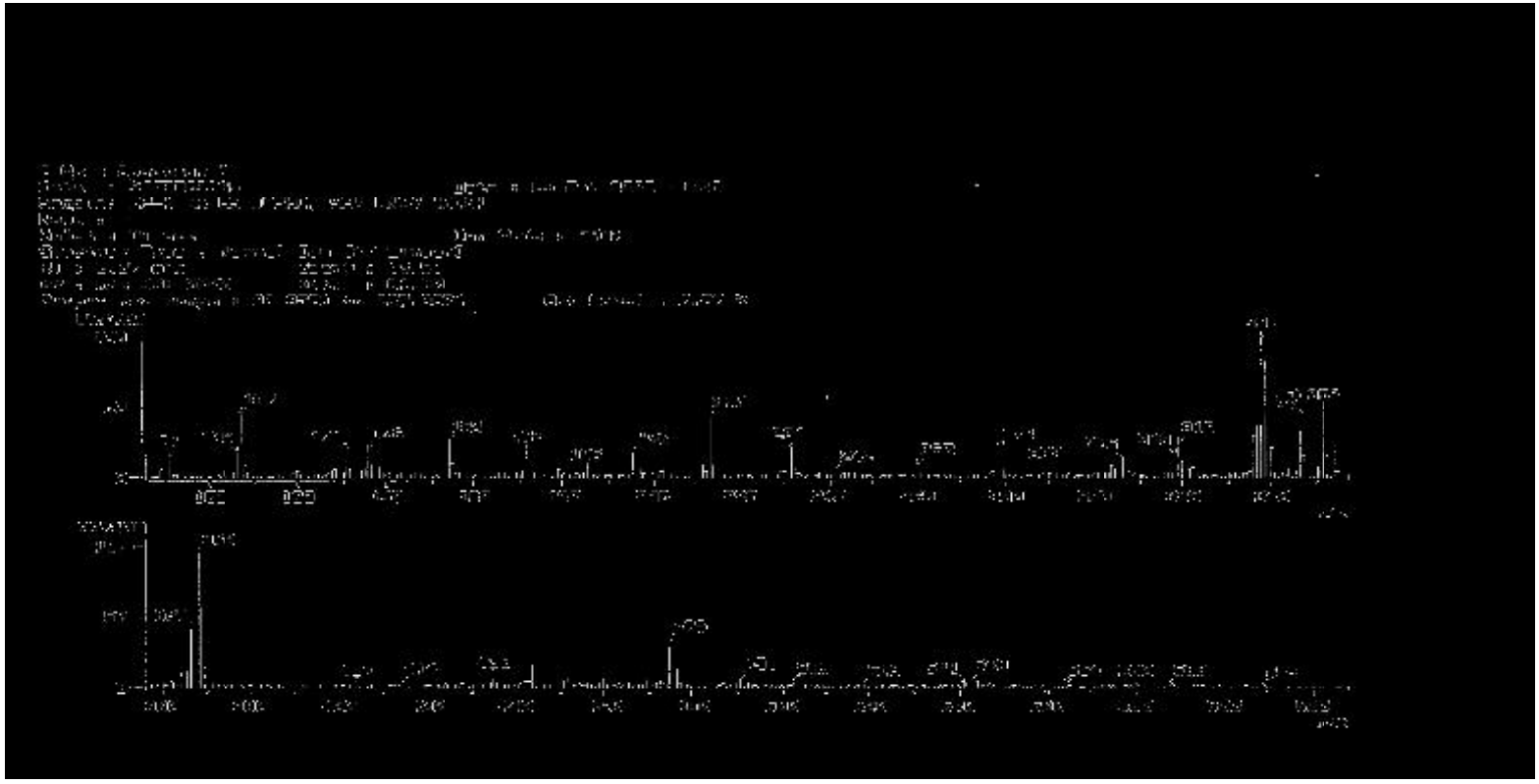
NMR SPECTRAL STUDIES OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.92	3H	singlet	Ar-OCH_3	-
2	5.75	1H	singlet	Ar-Hc	-
3	7.00-7.03	2H	doublet	Ar-Hb,b'	Jaa'=9.0
4	7.29-7.46	8H	multiplet	Ar-H	-
5	7.59-7.62	2H	doublet	Ar-Ha,a'	Jbb'=9.0
6	9.15	1H	singlet	-NH(Amide)	-

MASS SPECTRAL STUDIES OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES.

(A) Synthesis of Ethyl-3-(4-methoxyphenyl)-3-oxopropanoate.

See Part-I, Section-II (A).

(B) Synthesis of N-(2,4-Dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide.

A mixture of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate (2.22 gm, 0.01 mol) and 2,4-dichloro aniline (1.62 gm, 0.01 mol)) in ethanol was reflux for 10-12 hrs. The resulting solution was poured over crushed ice. The separated solid was filtered and crystallized from ethanol, Yield 71%, m.p.267 ^{0}C, Anal.Calcd. for $C_{16}H_{13}Cl_2NO_3$ Calcd: C, 56.32; H, 3.87; N, 4.14%, Found: C, 56.30; H, 3.86; N, 4.13%.

(C) Synthesis of N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one-5-carboxamide.

A mixture of N-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide (3.38 gm, 0.01 mol), urea (0.60 gm, 0.01 mol) and benzaldehyde (1.06 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^{0}C and the resulting solid mass separated was filtered and, crystallized from dioxane. Yield 39%, m.p.227 ^{0}C, Anal.Calcd. for $C_{24}H_{19}Cl_2N_3O_3$ Calcd: C, 61.55; H, 4.09; N, 8.97%, Found: C, 61.53; H, 4.08; N, 8.96%

Similarly, other N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxamides were prepared. The physical data are recorded in Table No.3

(C) Biological screening of N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-one-5-carboxamides.

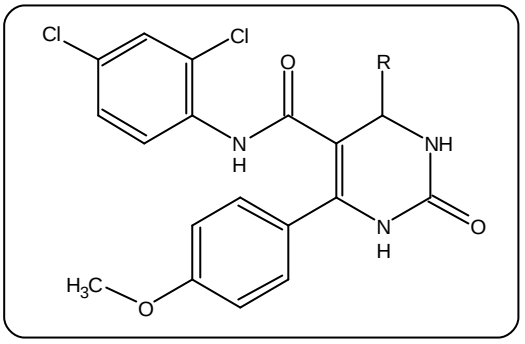
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.3

TABLE-3 : PHYSICAL CONSTANTS OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{0}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
3a	C_6H_5-	$C_{24}H_{19}Cl_2N_3O_3$	468	227	39	8.97	8.96	0.55	S1
3b	2-Cl-C_6H_4-	$C_{24}H_{18}Cl_3N_3O_3$	503	185	47	8.36	8.35	0.48	S2
3c	3-Cl-C_6H_4-	$C_{24}H_{18}Cl_3N_3O_3$	503	296	42	8.36	8.34	0.50	S1
3d	4-Cl-C_6H_4-	$C_{24}H_{18}Cl_3N_3O_3$	503	245	44	8.36	8.36	0.45	S1
3e	2-NO_2-C_6H_4-	$C_{24}H_{18}Cl_2N_4O_5$	513	224	31	10.91	10.90	0.52	S2
3f	3-NO_2-C_6H_4-	$C_{24}H_{18}Cl_2N_4O_5$	513	284	37	10.91	10.88	0.56	S2
3g	2-OH-C_6H_4-	$C_{24}H_{19}Cl_2N_3O_4$	484	214	47	8.68	8.65	0.32	S2
3h	4-OH-C_6H_4-	$C_{24}H_{19}Cl_2N_3O_4$	484	297	41	8.68	8.67	0.59	S2
3i	4-F-C_6H_4-	$C_{24}H_{18}FCl_2N_3O_3$	486	278	39	8.64	8.62	0.42	S1
3j	4-OCH_3 -C_6H_4-	$C_{25}H_{21}Cl_2N_3O_4$	498	315	37	8.43	8.41	0.44	S1
3k	2,5-$(OCH_3)_2$-C_6H_3-	$C_{26}H_{23}Cl_2N_3O_5$	528	301	48	7.95	7.94	0.54	S2
3l	4-$N(CH_3)_2$-C_6H_4-	$C_{26}H_{24}Cl_2N_4O_3$	511	227	54	10.96	10.95	0.43	S2

S1 Acetone:Benzene(1:9), S2 Hexane:Ethyl acetate(8:2)

ANTITUBERCULAR ACTIVITY OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES.



TAACF, Southern Research Insitute

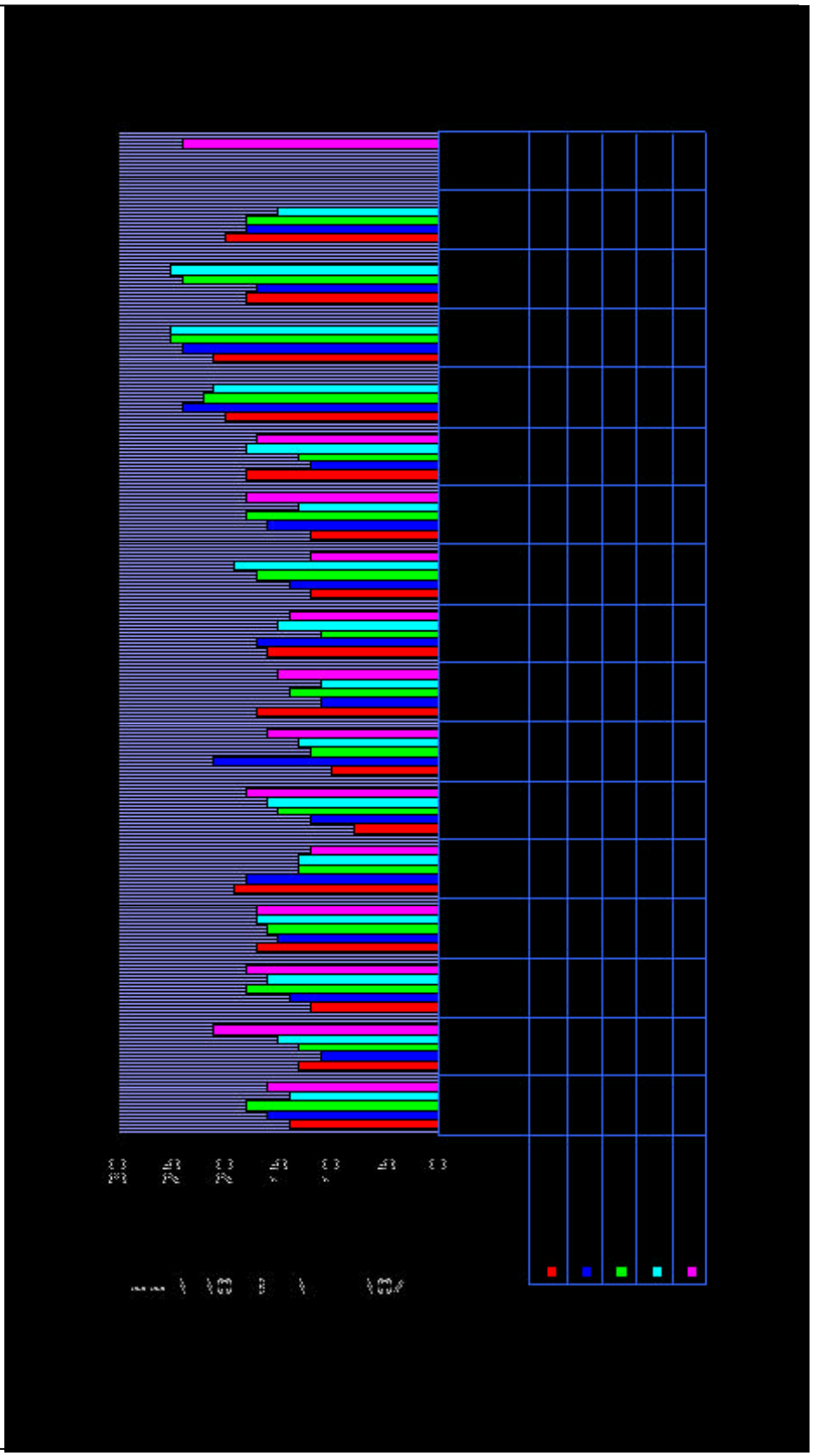
TABLE NO-3

Primary Assay Summary Report

Sr. No.	Sample ID	Corp ID	R	Assay	Mtb Strain	MIC mg/ml	% Inhibi.
3a	179663	ZP-27	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	52
3b	179664	ZP-28	2-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
3c	179665	ZP-29	3-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
3d	179666	ZP-30	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	12
3e	179667	ZP-31	2-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	65
3f	179668	ZP-32	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	45
3g	179669	ZP-33	4-CI-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	47
3h	179670	ZP-34	3-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
3i	179671	ZP-35	4-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
3j	179672	ZP-36	2,5-$(OCH_3)_2$-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	12
3k	179673	ZP-37	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
3l	179674	ZP-38	2-OH-4-OCH_3-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	25

NAID/Southern Research Insitute/GWL Hansen's Disease Centre/Colorado State University proprietary Information

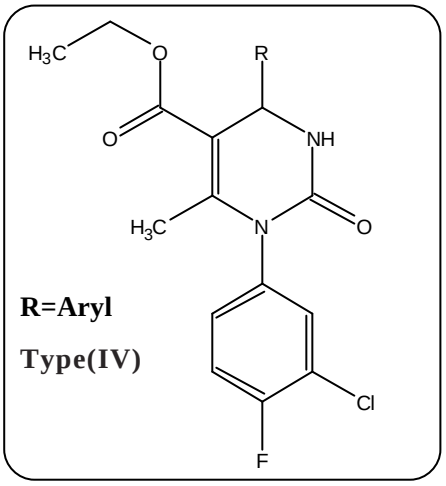
GRAPHICAL CHART NO. 3 : ANTIMICROBIAL ACTIVITY OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXY PHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-ONE-5-CARBOXAMIDES



SECTION - IV

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES.

The broad spectrums of pharmacological properties have been demonstrate by the dihydropyrimidinone nucleus.Inspired by these facts, novel dihydropyrimidinone derivatives of type(IV) have been synthesized by the condensation of ethylacetoacetate,N-(3-chloro-4-fluorophenyl)urea and aryl aldehydes.



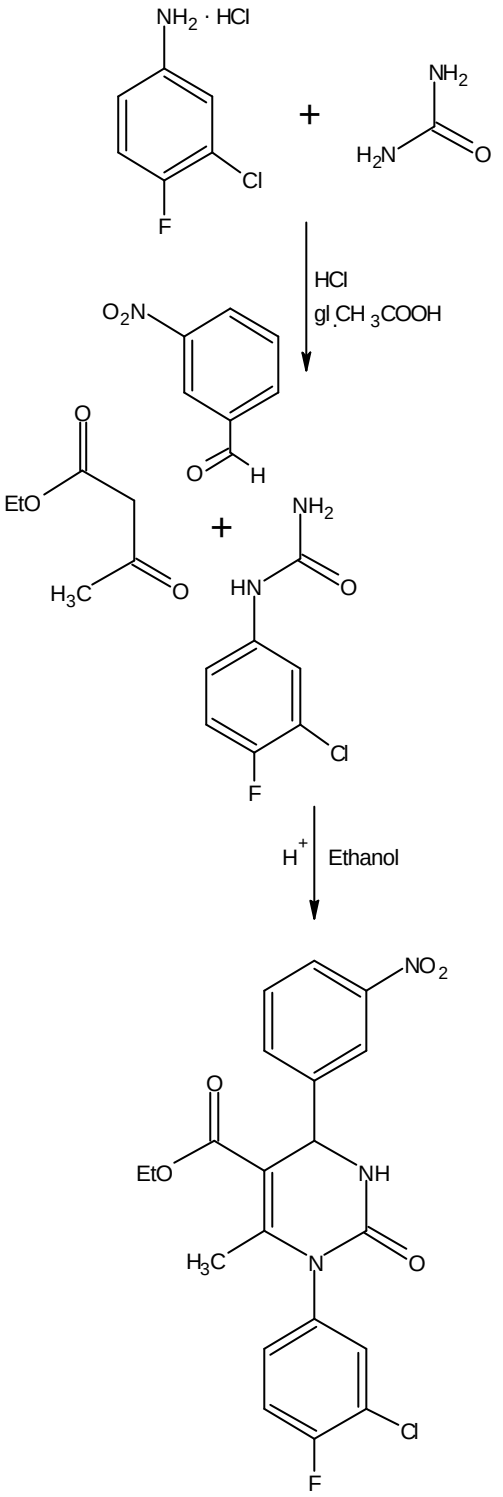
R=Aryl

Type(IV)

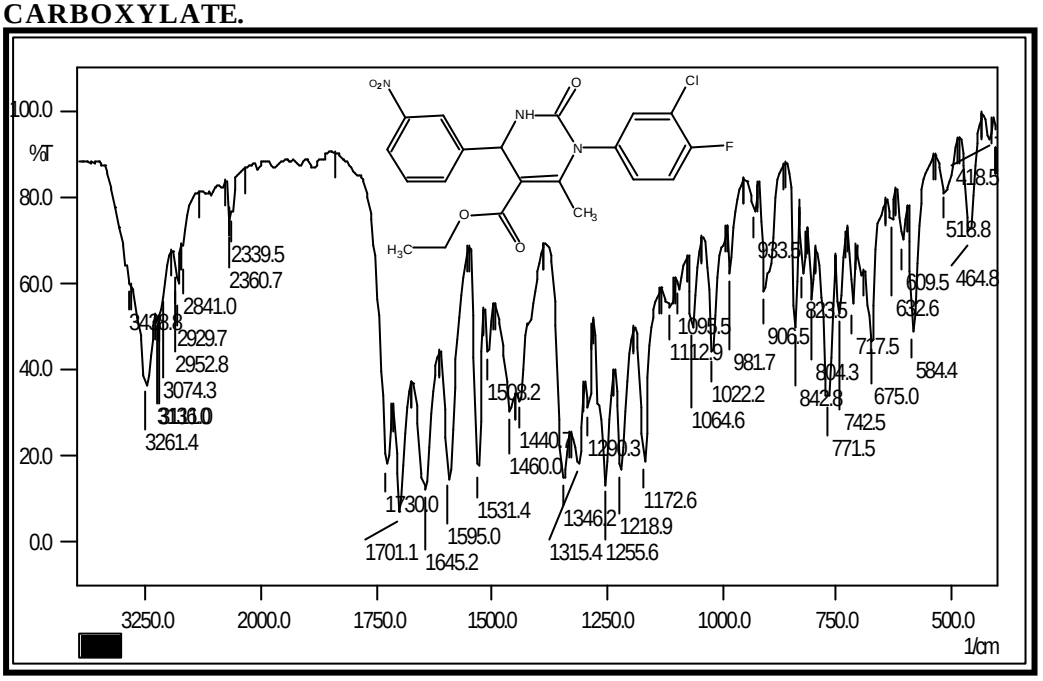
The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Reaction Scheme



IR SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-(3-NITROPHENYL)-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATE.

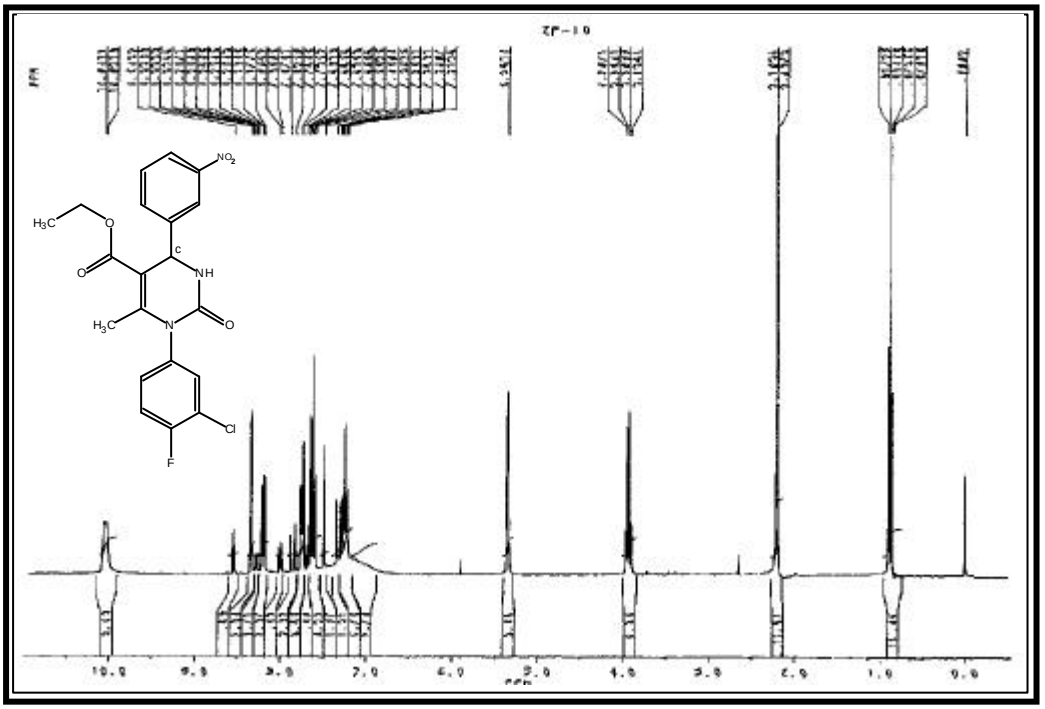


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}

(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2929	2975-2950	255
-CH_3	C-H str. (sym.)	2841	2880-2860	,,
	C-H i.p.def. (asym.)	1440	1470-1435	,,
	C-H o.o.p. def. (sym.)	1346	1390-1370	,,
Aromatic	C-H str.	3111	3090-3030	256
	C=C str.	1460	1540-1480	,,
	C-H i.p. (def.)	1095	1125-1090	,,
	C-H o.o.p. (def)	823	835-810	,,
Pyrimidine	C=C str.	1595	1580-1520	,,
moity	C-H str.	3074	3080-3030	,,
	C-H i.p. def.	1064	1125-1090	,,
Amine	-NH str.	3438	3410-3380	255
	-NH def.	1645	1635-1595	,,
Cabonyl	-C=O str.	1730	1700-1725	,,
Ester	- C=O str	1701	1690-1660	,,
Halide	-C-CI str.	742	700-750	,,

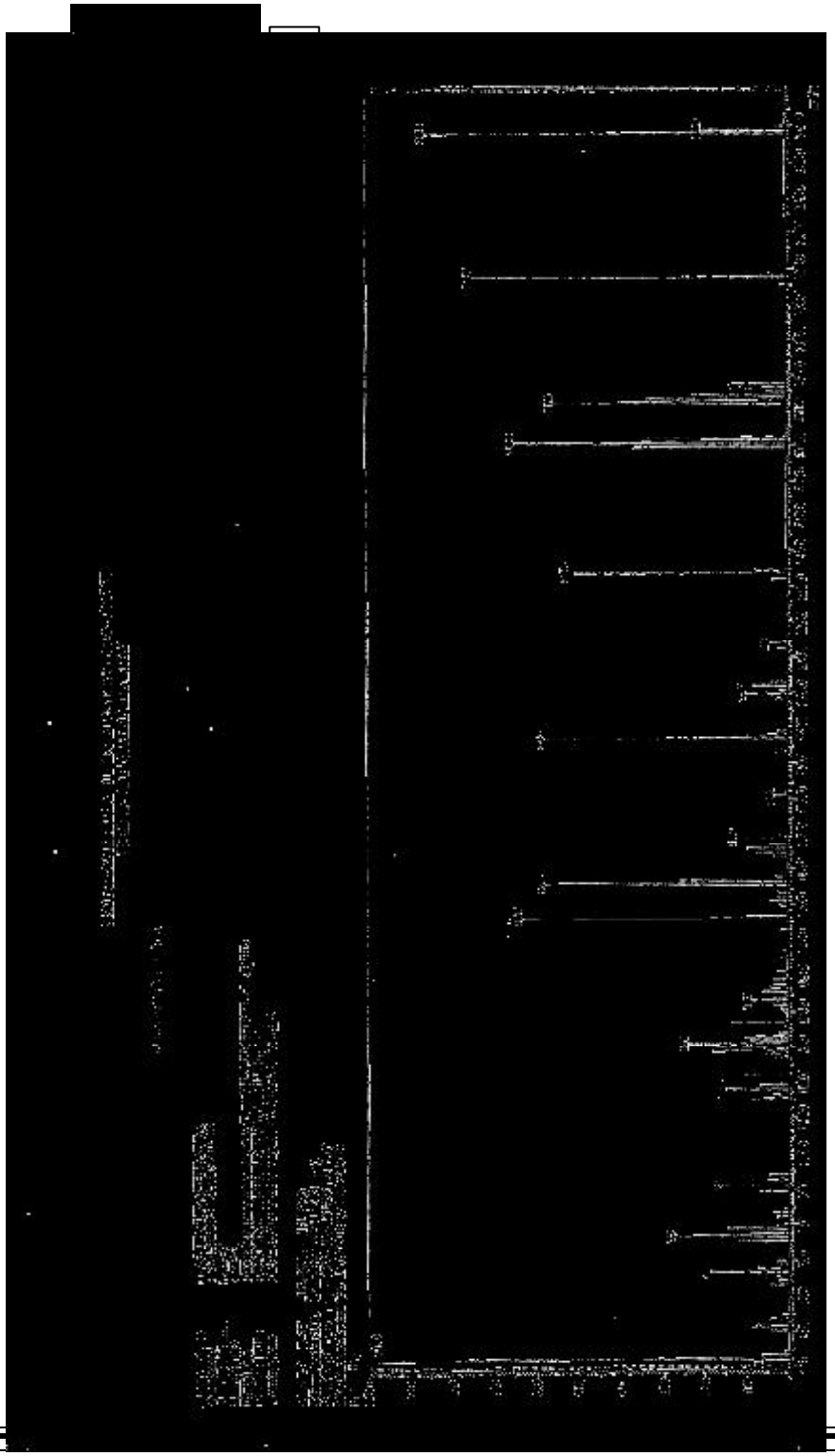
NMR SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-(3-NITROPHENYL)-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-ONE -5-CARBOXYLATE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	0.91	3H	triplet	$-CH_3$	-
2	2.10	3H	singlet	$Ar-CH_3$	-
3	4.07	2H	quatret	$-CH_2$	-
4	5.36	1H	singlet	Ar-Hc	-
5	7.21-8.51	7H	multiplet	Ar-H	-
6	10.04	1H	singlet	NH(Pyr.)	-

MASS SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)4-PHENYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES.

(A) Synthesis of N-(3-chloro-4-fluorophenyl)urea.

A mixture of 3-chloro-4-fluoroaniline hydrochloride (18.1 gm, 0.1 mol) and urea (24.0 gm, 0.4 mol) was placed in a 1-lit round-bottomed flask. To this mixture were added 40 ml of water,1 ml of concentrated hydrochloric acid and 1 ml of glacial acetic acid. The mixture was heated vigorously untill the entire contents of the vessel suddenly set to a solid mass. The source of heat is immediately withdrawn at this point. After cooling to room temperature, the product was broken up with the addition of water, filtered and washed with cold water. Yield 58%, m.p.228 ^{0}C , Anal.Calcd. for $C_7H_6ClFN_2O$ Calcd: C, 44.58; H, 3.21; N, 14.85%, Found: C, 44.57; H, 3.19; N, 14.84%.

(B) Synthesis of Ethyl-1-(3-chloro-4-fluorophenyl)-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylate.

A mixture of ethyl acetoacetate (1.30 gm, 0.01 mol), N-(3-chloro-4-fluorophenyl)urea (1.88 gm, 0.01 mol) and m-nitrobenzaldehyde (1.51 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O ^{0}C. The resulting solid mass separated was filtered and, crystallized from dioxane. Yield 51%, m.p.268 ^{0}C, Anal.Calcd. for $C_{20}H_{17}ClFN_3O_5$ Calcd: C, 55.37; H, 3.95; N, 9.69%, Found: C, 55.35; H, 3.94; N, 9.67%.

Similarly, other Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates were prepared. The physical data are recorded in Table No.4

(C) Biological screening of Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-one-5-carboxylates.

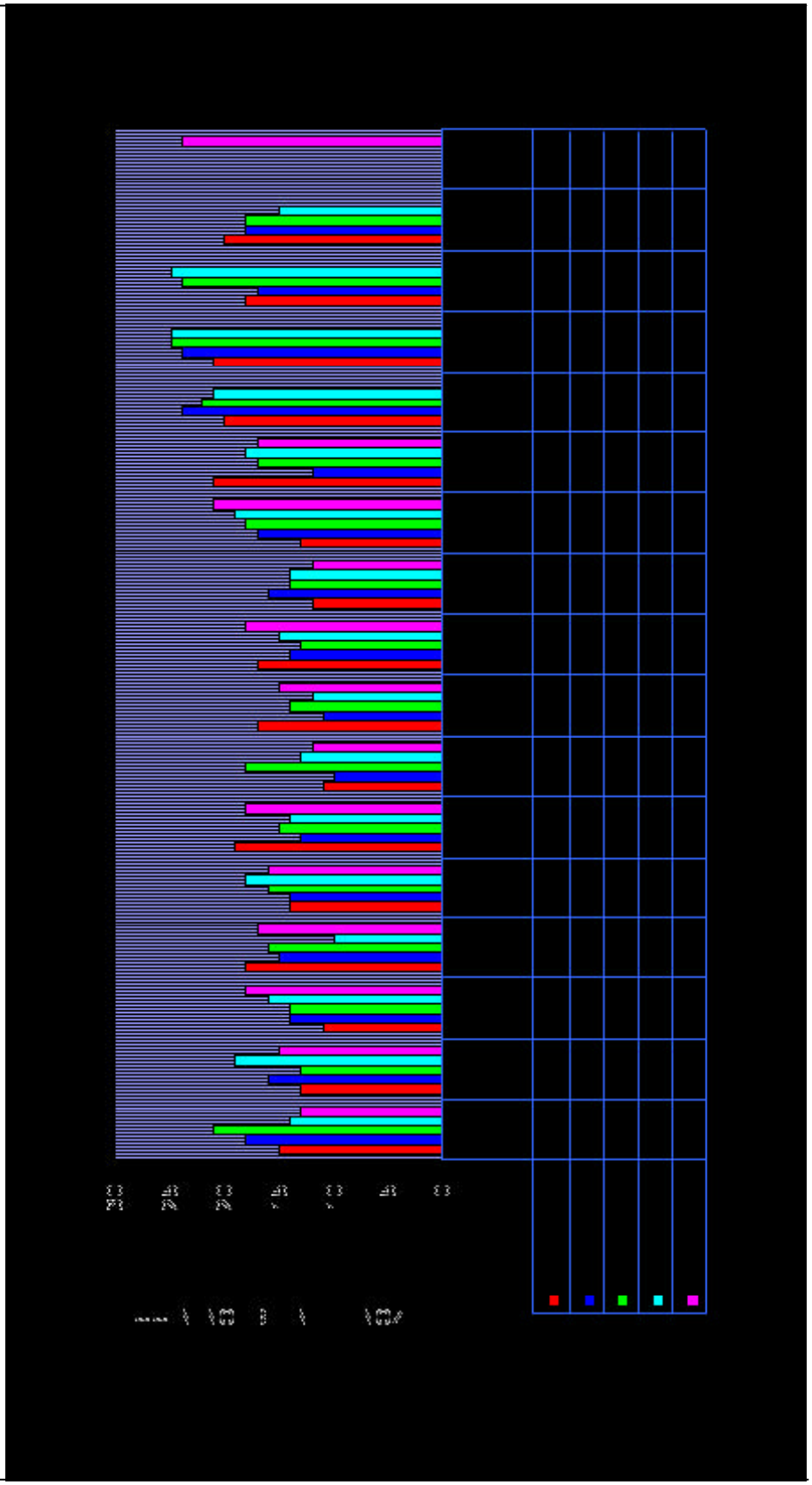
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.4

TABLE-4 : PHYSICAL CONSTANTS OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
4a	C_6H_5-	$C_{20}H_{18}ClFN_2O_3$	388	235	32	7.20	7.17	0.55	S1
4b	2-Cl-C_6H_4-	$C_{20}H_{17}Cl_2FN_2O_3$	423	213	46	6.62	6.60	0.48	S2
4c	3-Cl-C_6H_4-	$C_{20}H_{17}Cl_2FN_2O_3$	423	214	41	6.62	6.61	0.50	S1
4d	2-NO_2-C_6H_4-	$C_{20}H_{17}ClFN_3O_5$	434	287	39	9.69	9.68	0.45	S1
4e	3-NO_2-C_6H_4-	$C_{20}H_{17}ClFN_3O_5$	434	268	51	9.69	9.67	0.52	S2
4f	4-F-C_6H_4-	$C_{20}H_{17}ClF_2N_2O_3$	407	201	47	6.89	6.87	0.56	S2
4g	4-OCH_3-C_6H_4-	$C_{21}H_{20}ClFN_2O_4$	419	247	34	6.69	6.88	0.32	S2
4h	2,5-$(OCH_3)_2$-C_6H_3-	$C_{22}H_{22}ClFN_2O_5$	449	284	37	6.24	6.21	0.59	S2
4i	2-OH-C_6H_4-	$C_{20}H_{18}CIFN_2O_4$	405	310	34	6.92	6.90	0.42	S1
4j	2-OH,4-OCH_3 -C_6H_3-	$C_{21}H_{20}ClFN_2O_5$	435	287	41	6.44	6.43	0.44	S1
4k	4-OH-C_6H_4-	$C_{20}H_{18}ClFN_2O_4$	405	321	48	6.92	6.91	0.54	S2
4l	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{23}ClFN_3O_3$	432	325	41	9.73	9.72	0.43	S2

S1Acetone:Benzene(1:9), S2 Hexane:Ethyl acetate(7:3)

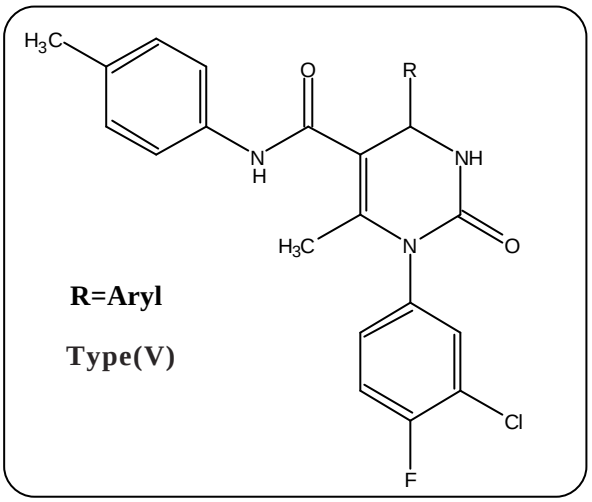
GRAPHICAL CHART NO. 4 : ANTIMICROBIAL ACTIVITYS OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES



SECTION - V

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXAMIDES.

N^1-substituted dihydropyrimidinone play vital role owing to their range of biological and physiological activities.In the light of these biological activities and variety of industrial applications,some new N^1-substituted dihydropyrimidinone derivatives of Type (V) have been synthesized by the condensation N-(4-methylphenyl)-3-oxobutanamide with N-(3-chloro-4-fluorophenyl)urea and aryl aldehydes



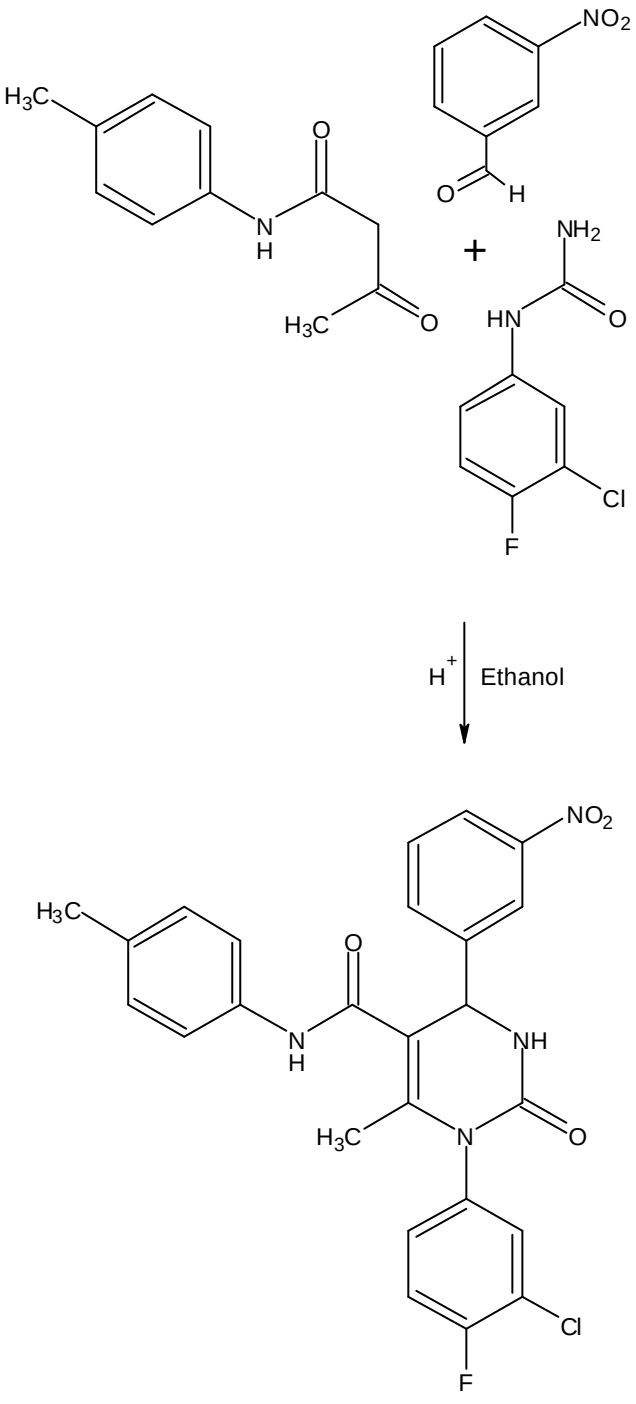
R=Aryl

Type(V)

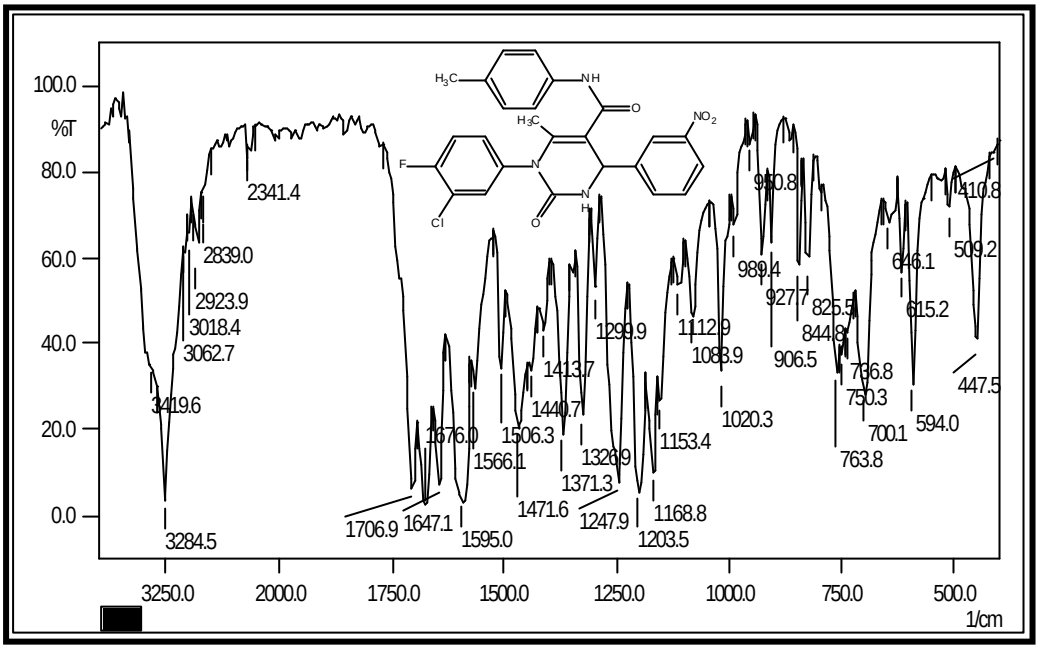
The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Reaction Scheme



IR SPECTRAL STUDIES OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-(3-NITROPHENYL)-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXAMIDE.

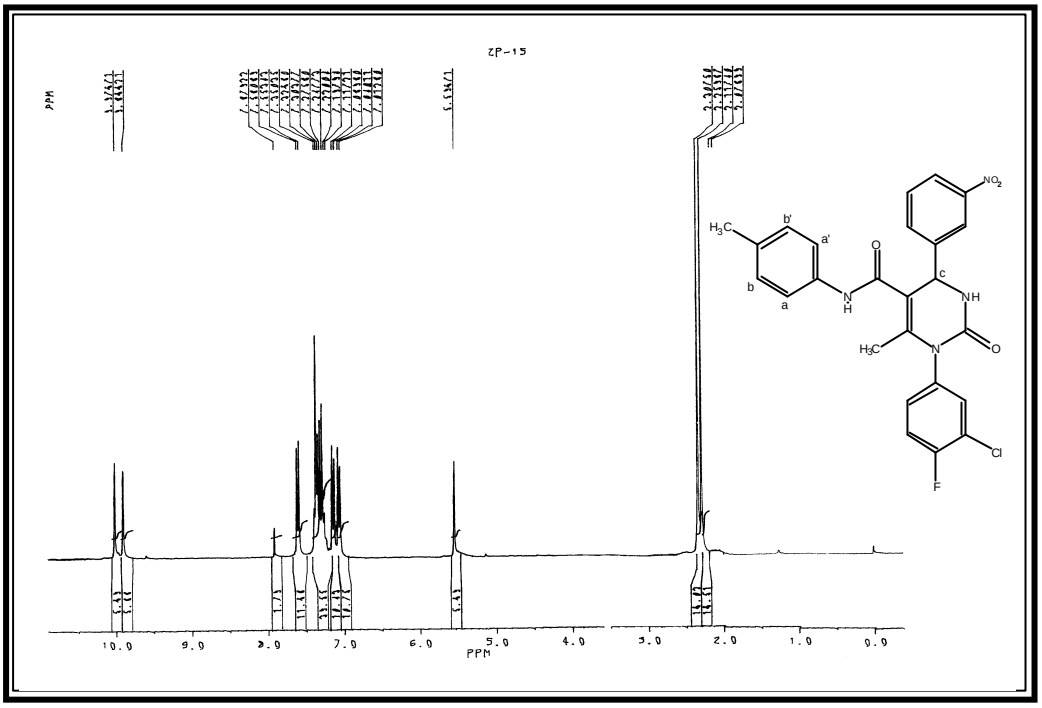


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}

(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2923	2975-2950	255
-CH_3	C-H str. (sym.)	2839	2880-2860	,,
	C-H i.p.def. (asym.)	1440	1470-1435	,,
	C-H o.o.p. def. (sym.)	1371	1390-1370	,,
Aromatic	C-H str.	3062	3090-3030	256
	C=C str.	1471	1540-1480	,,
	C-H i.p. (def.)	1083	1125-1090	,,
	C-H o.o.p. (def)	825	835-810	,,
Pyrimidine	C=C str.	1566	1580-1520	,,
moity	C-H str.	3018	3080-3030	,,
	C-H i.p. def.	1153	1125-1090	,,
Amine	-NH str.	3419	3410-3380	255
	-NH def.	1647	1635-1595	,,
Cabonyl	-C=O str.	1706	1700-1725	,,
Amide	- C=O str	1678	1690-1660	,,
Halide	-C-CI str.	736	700-750	,,

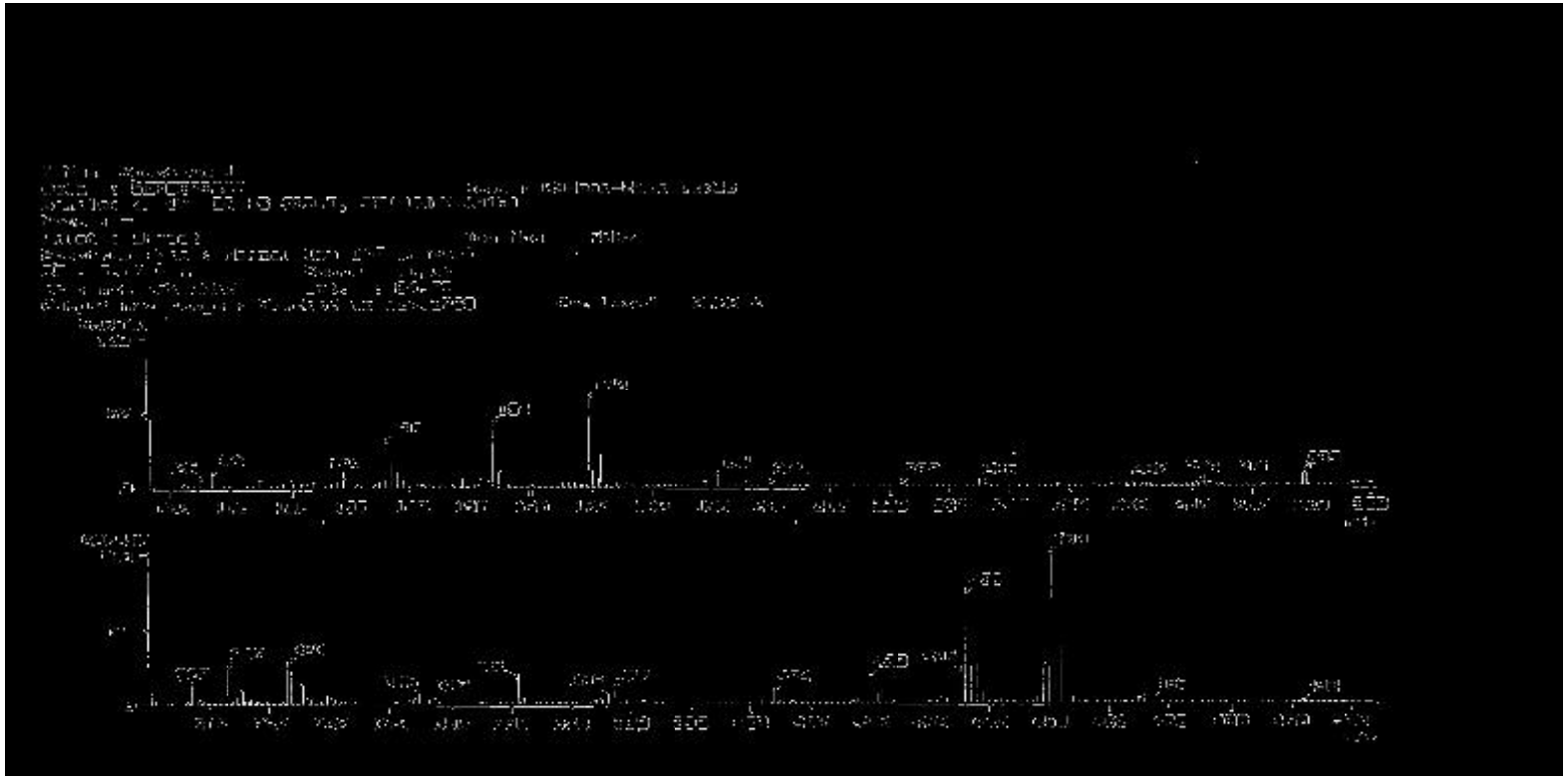
NMR SPECTRAL STUDIES OF 1-(3-CHLORO-4-FLUORPHENYL)-4-(3-NITROPHENYL)-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDRO PYRIMIDIN-2-ONE-5-CARBOXAMIDE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.25	3H	singlet	-CH_3(Pyr.)	-
2	2.30	3H	singlet	Ar-CH_3	-
3	5.59	1H	singlet	Ar-Hc	-
4	7.01-7.04	2H	doublet	Ar-Ha,a'	Jaa'=9.0
5	7.08-7.35	7H	multiplate	Ar-H	-
6	7.55-7.58	2H	doublet	Ar-Hb,b'	Jbb'=9.0
7	9.86	1H	singlet	-NH(Amide)	-
8	9.97	1H	singlet	-NH(Pyr.)	-

MASS SPECTRAL STUDIES OF 1-(3-CHLORO-4-FLUORPHENYL)-4-PHENYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXAMIDE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXAMIDES.

(A) Synthesis of N-(4-methylphenyl)-3-oxobutanamide.

See Part-I, Section-I (A).

(B) Synthesis of N-(3-chloro-4-fluorophenyl)urea.

See Part-I, Section-IV (A).

(C) Synthesis of 1-(3-Chloro-4-fluorophenyl)-4-(3-nitrophenyl)-6-methyl-N-(4-methylphenyl)-3,4-dihydropyrimidin-2-one-5-carboxamide.

A mixture of N-(4-methyl phenyl)-3-oxobutanmide (1.91 gm, 0.01 mol), N-(3-chloro-4-fluorophenyl)urea (1.88 gm, 0.01 mol) and m-nitrobenzaldehyde (1.51 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The resulting solution was allowed to stand for 12 hrs. at O^0C, thus the solid mass separated was filtered and crystallized from dioxane. Yield 38%, m.p.305 ^{0}C, Anal.Calcd. for $C_{25}H_{20}CIFN_4O_4$ Calcd: C, 60.67; H, 4.07; N, 11.32%, Found: C, 60.66; H, 4.05; N, 11.31%.

Similarly, other 1-(3-Chloro-4-fluorophenyl)-4-aryl-6-methyl-N-(4-methylphenyl)-3,4-dihydropyrimidin-2-one-5-carboxamides were prepared. The physical data are recorded in Table No.5

(D) Biological screening of 1-(3-Chloro-4-fluorophenyl)-4-aryl-6-methyl-N-(4-methylphenyl)-3,4-dihydropyrimidin-2-one-5-carboxamides.

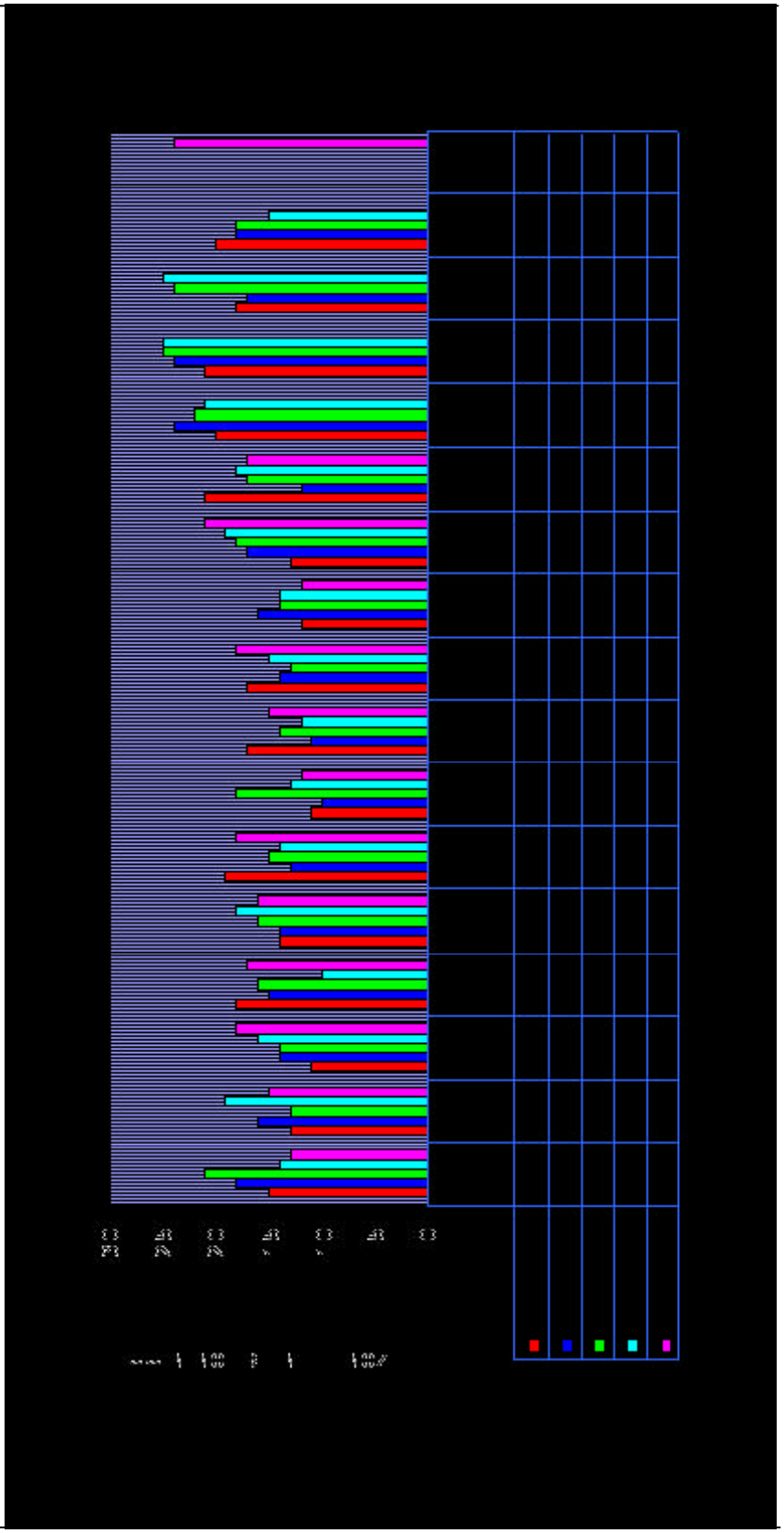
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.5

TABLE-5 : PHYSICAL CONSTANTS OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYL PHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
5a	C_6H_5-	$C_{25}H_{21}ClFN_3O_2$	450	301	41	9.34	9.33	0.52	S1
5b	2-Cl-C_6H_4-	$C_{25}H_{20}Cl_2FN_3O_2$	484	258	47	8.68	8.67	0.46	S2
5c	3-Cl-C_6H_4-	$C_{25}H_{20}Cl_2FN_3O_2$	484	254	46	8.68	8.66	0.59	S2
5d	2-NO_2-C_6H_4-	$C_{25}H_{20}ClFN_4O_4$	495	212	41	11.32	11.30	0.48	S1
5e	3-NO_2-C_6H_4-	$C_{25}H_{20}ClFN_4O_4$	495	305	38	11.32	11.31	0.55	S2
5f	4-F-C_6H_4-	$C_{25}H_{20}ClF_2N_3O_2$	468	287	41	8.98	8.97	0.52	S1
5g	4-OCH_3 -C_6H_4-	$C_{26}H_{23}ClFN_3O_3$	480	262	47	8.76	8.75	0.39	S2
5h	2,5-$(OCH_3)_2$-C_6H_3-	$C_{27}H_{25}ClFN_3O_4$	510	214	42	8.24	8.21	0.54	S1
5i	2-OH-C_6H_4-	$C_{25}H_{21}CIFN_3O_3$	466	321	47	9.02	9.01	0.48	S2
5j	4-OH-C_6H_4-	$C_{25}H_{21}ClFN_3O_3$	466	289	35	9.02	9.01	0.45	S1
5k	2-OH,4-OCH_3 -C_6H_3-	$C_{26}H_{23}ClFN_3O_4$	496	302	54	8.47	8.46	0.52	S2
5l	4-$N(CH_3)_2$-C_6H_4-	$C_{27}H_{26}ClFN_4O_2$	493	254	48	11.37	11.35	0.40	S2

S1Acetone:Benzene(2:8), S2Acetone:Benzene(1:9)

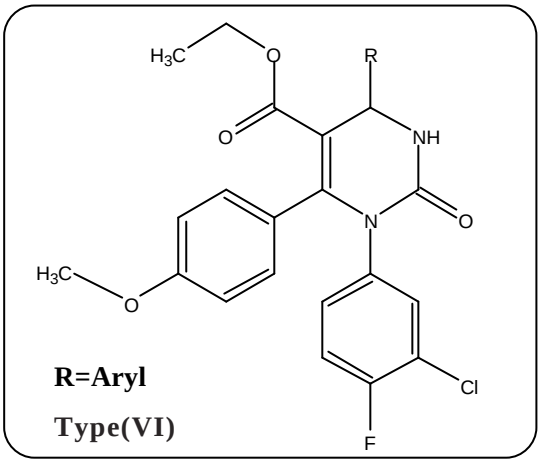
GRAPHICAL CHART NO. 5: ANTIMICROBIAL ACTIVITY OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXAMIDES



SECTION - VI

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES.

Dihydropyrimidinone derivatives represent one of the most classes of compound having a wide spectrum of biological activities.With an aim to get better therapeutic agent the dihydropyrimidinone derivatives of type (VI) have been synthesized by the condensation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate, N-(3-chloro-4-fluorophenyl)urea and aryl aldehydes.



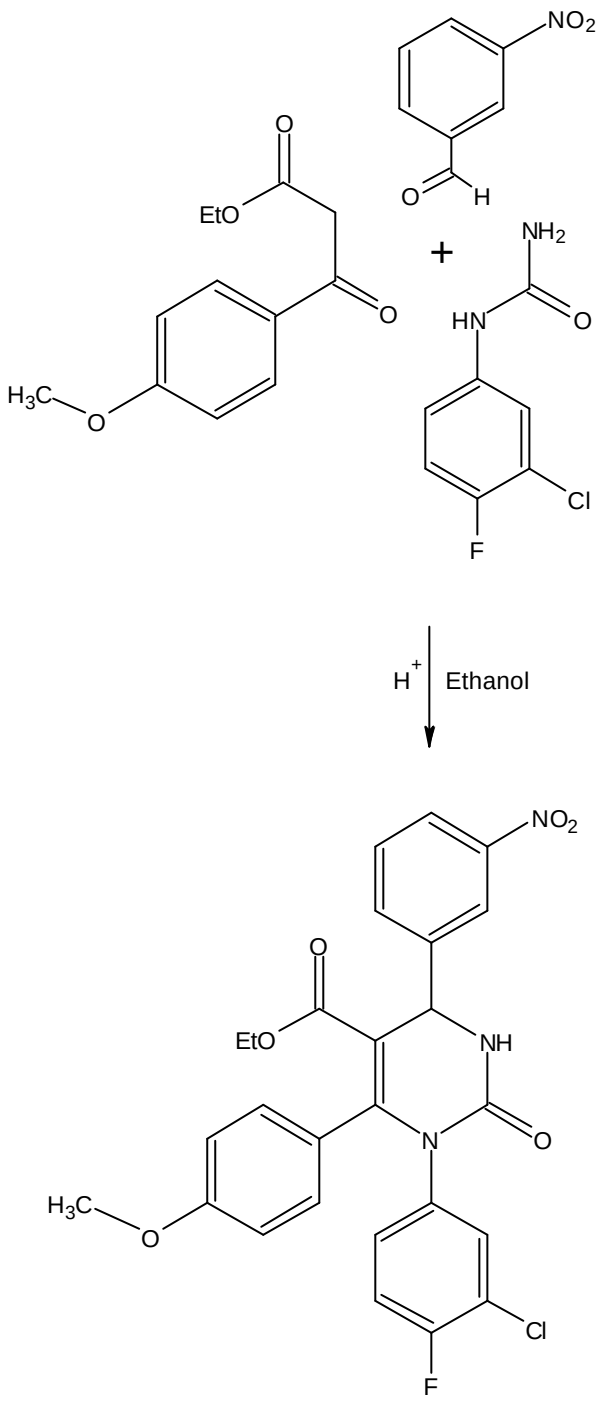
R=Aryl

Type(VI)

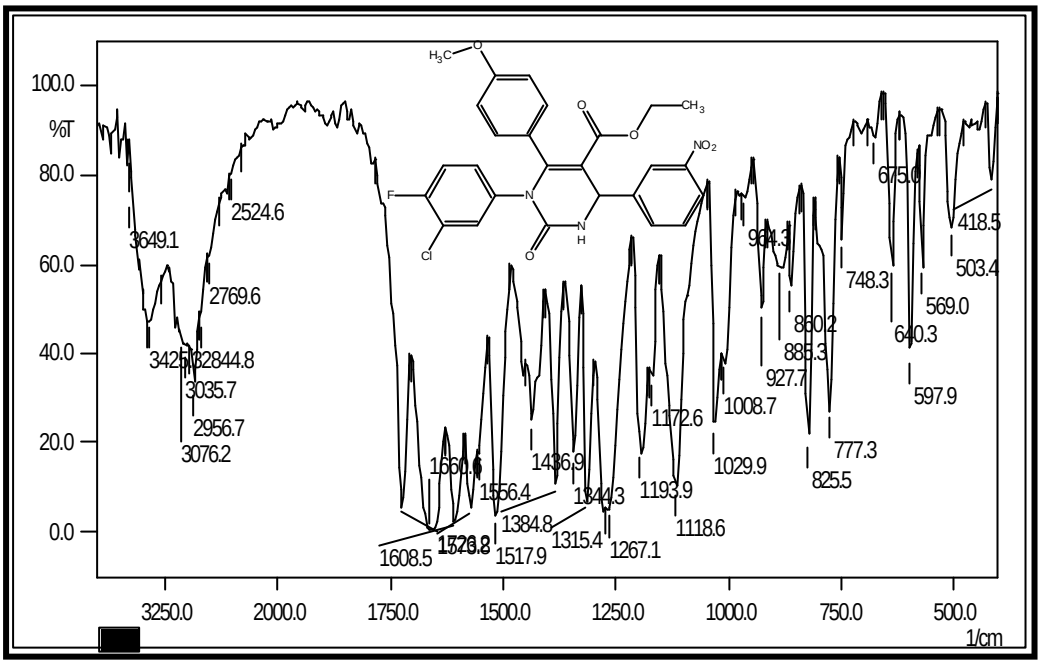
The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Reaction Scheme



IR SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUORO PHENYL)-4-(3-NITROPHENYL)-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATE.

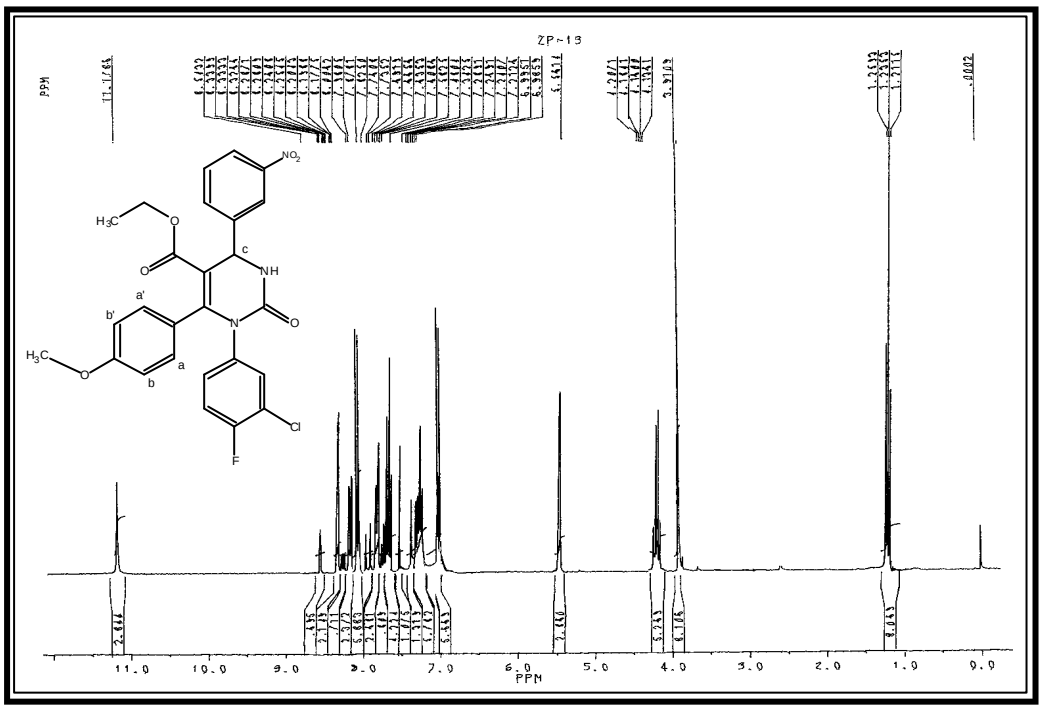


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}

(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2956	2975-2950	255
-CH_3	C-H str. (sym.)	2844	2880-2860	,,
	C-H i.p.def. (asym.)	1437	1470-1435	,,
	C-H o.o.p. def. (sym.)	1344	1390-1370	,,
Aromatic	C-H str.	3035	3090-3030	256
	C=C str.	1465	1540-1480	,,
	C-H i.p. (def.)	1118	1125-1090	,,
	C-H o.o.p. (def)	825	835-810	,,
Pyrimidine	C=C str.	1556	1580-1520	,,
moity	C-H str.	3074	3080-3030	,,
	C-H i.p. def.	1172	1125-1090	,,
Amine	-NH str.	3425	3410-3380	255
	-NH def.	1608	1635-1595	,,
Cabonyl	-C=O str.	1726	1700-1725	,,
Ester	- C=O str	1660	1690-1660	,,
Halide	-C-CI str.	777	700-750	,,

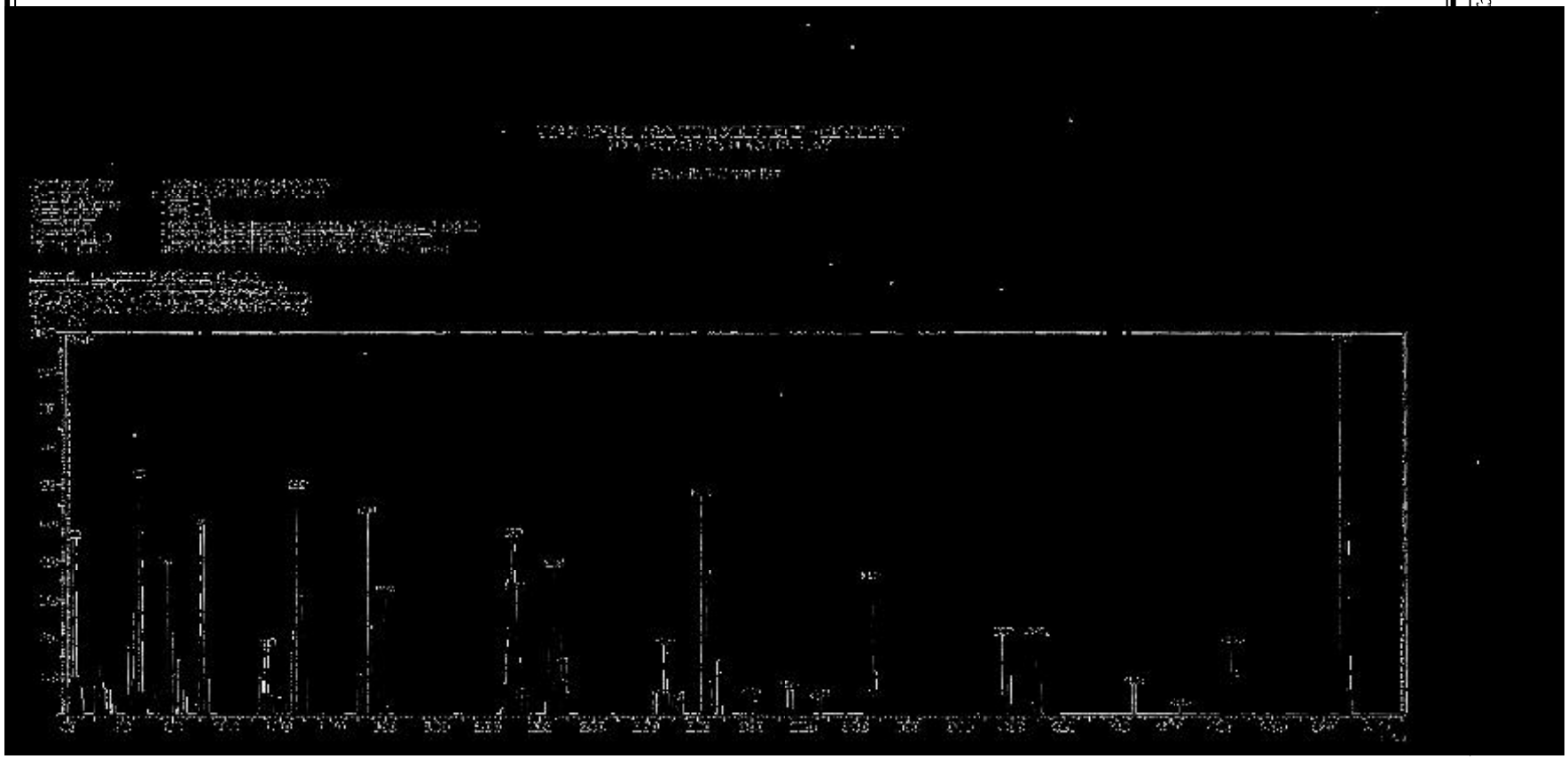
NMR SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUORO PHENYL)-4-(3-NITROPHENYL)-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.23	3H	triplet	$-CH_3$	-
2	3.91	3H	singlet	$Ar-OCH_3$	-
3	4.16	2H	quatret	$-CH_2$	-
4	5.56	1H	singlet	Ar-Hc	-
5	6.99-7.02	2H	doublet	Ar-Hb,b'	Jaa'=9.0
6	7.21-8.33	7H	multiplet	Ar-H	
7	8.06-8.09	2H	doublet	Ar-Ha,a'	Jbb'=9.0
8	11.17	1H	singlet	NH(Pyr.)	-

MASS SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-(3-NITROPHENYL)-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES.

(A) Synthesis of Ethyl-3-(4-methoxyphenyl)-3-oxopropanoate.

See Part-I, Section-II (A).

(B) Synthesis of N-(3-chloro-4-fluorophenyl)urea.

See Part-I, Section-IV (A).

(C) Synthesis of Ethyl-1-(3-chloro-4-fluorophenyl)-4-(3-nitrophenyl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2-one-5-carboxylate.

A mixture of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate (2.22 gm, 0.01 mol), N-(3-chloro-4-fluorophenyl)urea (1.88 gm, 0.01 mol) and m-nitrobenzaldehyde (1.51 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^0C. The resulting solid mass separated was filtered and, crystallized from dioxane. Yield 45%, m.p.221^{0}C, Anal.Calcd. for $C_{26}H_{21}CIFN_3O_6$ Calcd: C, 59.38; H, 4.02; N, 7.99%, Found: C, 59.35; H, 4.01; N, 7.98%.

Similarly, other Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2-one-5-carboxylates were prepared. The physical data are recorded in Table No.6

(D) Biological screening of Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2-one-5-carboxylates.

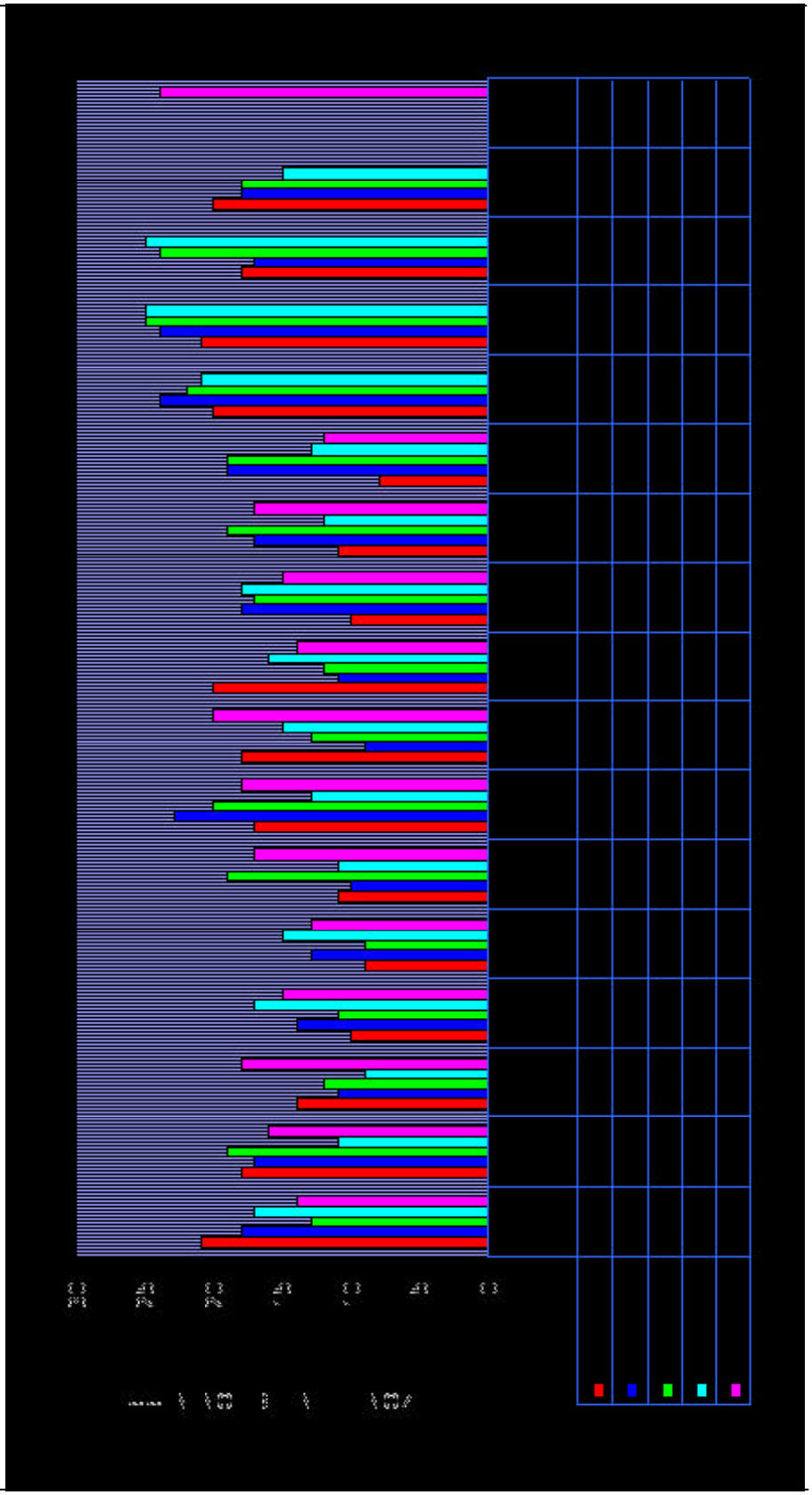
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.6

TABLE-6 : PHYSICAL CONSTANTS OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
6a	C_6H_5-	$C_{26}H_{22}ClFN_2O_4$	481	304	31	5.83	5.82	0.59	S1
6b	2-Cl-C_6H_4-	$C_{26}H_{21}Cl_2FN_2O_4$	515	145	41	5.44	5.42	0.45	S2
6c	3-Cl-C_6H_4-	$C_{26}H_{21}Cl_2FN_2O_4$	515	309	47	5.44	5.43	0.51	S1
6d	4-Cl-C_6H_4-	$C_{26}H_{21}Cl_2FN_2O_4$	515	254	35	5.44	5.43	0.42	S2
6e	4-F-C_6H_4-	$C_{26}H_{21}ClF_2N_2O_4$	499	214	38	5.61	5.60	0.53	S2
6f	2-NO_2-C_6H_4-	$C_{26}H_{21}ClFN_3O_6$	526	287	37	7.99	7.97	0.55	S2
6g	3-NO_2-C_6H_4-	$C_{26}H_{21}ClFN_3O_6$	526	221	45	7.99	7.98	0.38	S1
6h	4-OCH_3 -C_6H_4-	$C_{27}H_{24}ClFN_2O_5$	511	247	47	5.48	5.47	0.54	S2
6i	2,5-$(OCH_3)_2$-C_6H_3-	$C_{28}H_{26}CIFN_2O_6$	541	305	45	5.18	5.17	0.42	S2
6j	4-OH -C_6H_4-	$C_{26}H_{22}ClFN_2O_5$	497	254	41	5.64	5.62	0.57	S1
6k	2-OH,4-OCH_3 -C_6H_3-	$C_{27}H_{24}ClFN_2O_6$	527	214	50	5.32	5.30	0.54	S2
6l	4-$N(CH_3)_2$-C_6H_4-	$C_{28}H_{27}ClFN_3O_4$	524	227	57	8.02	8.01	0.48	S2

S1 Hexane:Ethyl acetate(3:7), S2Acetone:Benzene(1:9)

GRAPHICAL CHART NO. 6 : ANTIMICROBIAL ACTIVITY OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-ONE-5-CARBOXYLATES



REFERENCES :

1 Weis, A. L.
Adv. Heterocycl. Chem. **38,** 1 (1985).

2 Yasui, S.; Nakamura, K.; Ohno, A.
J. Org. Chem., **49,** 878 (1984).

3 Baba, N.;Amano, M.; Oda, J.; Inouye, Y.
*J. Am. Chem. Soc.***106,** 1481 (1984). *Annular Reports in Medicinal Chemistry.* **19,** 119 (1984).

4 Eisner, U.; Kuthan, J.
J. Chem. Reu. **72,** 1 (1972).

5 Kuthan, J.; Kurfurst, A.
Jnd. Eng. Prod. Res. Deu. **21,** 191 (1982).

6 Stout, D. M.; Meyers, A. I.
J. Chem. Reu. **82,** 223 (1982).

7 Bossert, F.; Vater, W.
Naturwissenshaften **58,** 578 (1971).

8 Vater,W.; Kronenberg, G.; Hoffmeister, F.; Keller, H.; Meng, A,; Oberdorf, A.; Puls, W.; Schlossmann, K.; Stoepel, K.
Arzneim. Forsch. **22,** 1 (1972).

9 Loev, B.; Goodman, M. M.; Snader, K. M.; Tedeschi, R.; Macko, E.
J. Med. Chem. **17,** 956 (1974).

10 Stone, P. H.
J. Cardiouasc. Med. **7,**181 (1982).

11 Bossert, F.; Meyer, H.; Wehinger, E.
Angew. Chem., Int. Ed. Engl. **20,** 762 (1981).

12 Bodor, N. In *Design of Biopharmaceutical Properties Through Prodrugs and Analogs;* Roche, E. B., Ed.; American Pharmaceutical Association: Washington, DC, 1977; p 98.

13 Weis, A. L.; van der Plas, H. C.
Heterocycles. **24,** 1433 (1986).

14 Brown, D. J. In *The Chemistry of Heterocyclic Compounds;* Weissberger, A., Ed.; Wiley (Interscience): New York, (1962). Brown, D. J. In *The Chemistry of Heterocyclic Compounds,* Suppl. 1; Weissberger, A.; Ed.; Wiley: New York, (1970).

15 A. L. Weis, F. Frolow, R. Vishkautsan.
J. Org. Chem. **51,** 4623-4626 (1986).

16 Weis, A. L.; Vishkautsan, R.
Heterocycles **23,** 1077 (1985).

17 van der Stoel, R. E.; van der Plas, H. C.
J. Chem. SOC., Perkin Trans. **1,** 1288 (1979).

18 van der Stoel, R. E.; van der Plas, H. C.
J. Chem. Soc., *Perkin Trans.* **1,** 2393 (1979).

19 Minkin, Y. I.; Olekhnovich, L. P.; Zhdanov, Y. A.
Acc. Chem. Res.**14**, 210 (1981).

20 Weis, A. L.
Synthesis. 528 (1985).

21 Weis, A. L.; Frolow, F.
J. Chem. Soc., Perkin Trans. **1,** 83 (1986).

22 Weis, A. L.; Vishkautsan, R.
Isr. J. Chem.,in press.

23 Weis, A. L.
Tetrahedron lett. **23,** 449 (1982).

24 Weis, A. L.; Porat,Z;Luz.
J. Am. Chem Soc. **106,** 8021 (1984).

25 Paquette, L. A.
Angew. Chem., Int. Ed. Engl. **7,** 565 (1968).

26 Paquette,L. A.
Acc. Chem. Res. **6,** 393 (1973).

27 Armond, J.; Chekir, K.; Pinson, J.
Can. J. Chem. **52,**3971 (1974).

28 Biginelli P.
Uazz.Chim. Ital., **23,** 360-416 (1893).

29 Lu, J; Ma. H. R.
Synlett., 63-64 (2000).

30 Salehi Peyman; Dabiri Minoo; Zolfigol Mohammad Ali; Bodughai Fard.
Tetrahedron Letters., **44(14)** 2889-2891 (2003). *Chem. Abstr.,* **139,** 85298 (2003).

31 Sabitha Gowravarum; Reddy G.S.; Kirankumar; Reddy Ch. Srinivas; Yadav J. S.
Sunlett., **(6),** 858-860 (2003). *Chem. Abstr.,* **139,** 149600 (2003).

32 Foroughifar N.; Mobinikhaledi A.;Jirandehi H. Fathinejad.
Phosphorus. Sulfur and Silicon and the related elements., **178(3),** 495-500 (2003).
Chem. Abstr., **139,** 164767 (2003).

33 Yang Ling; Guo Yanhong; Lu Jun; Bai Yinjuna.
Huaxae Yanjia Yu Yingyong., **14(6),** 710-711 (2002). *Chem. Abstr.,* **139,** 180029 (2003).

34 Xia Min; Wang Yan-guang.
Synthesis., **2,** 262-266 (2003). *Chem. Abstr.,* **139,** 52969 (2003).

35 Fu Nan-Yan; Yang Yao-Fang; Pang Mei-Li; Wang Ji-Tao.
Gaodeng Xuexiao Huaxae Xuebao., **24(1),** 79-81 (2003). *Chem. Abstr.,* **139,** 197444 (2003).

36 Cao Znong; Wang Shan-Wei; Fu Nan-Yan; Yang Yao-Fang; Wang Ji-Tao.
Tetrahedron. **58(24),** 4801-4807 (2002).

37 Tu Shu-Jiang; Fang Fang; Niao Chun-Bao; Jiang Hong; Shi-Da-Qing.
Chines Journal of Chemistry., **21(6),** 706-709 (2003). *Chem. Abstr.,* **139,** 261241 (2003).

38 Tu Shujang; Shi Datqing; Wang Xiamgshan.
Tetrahedron Letters. **44(32),** 6153-6155 (2003). *Chem. Abstr.,* **139,** 261244 (2003).

39 Bigi F; Carloni S; Frullanti B; Muggi R; Sartori G.
Tetrahedron Letters., **40,** 3465 (1999).

40 Haixia Lin; Jinchang Bing; Xianten Chen; Ziyi Zhang.
Molecules., **5,** 1240-1243 (2000).

41 Subhas D. Bose; Liyakat Fatims; Hari Babu.
J. Org. Chem., **68,** 587-590 (2003).

42 Ranu C.; Alakananda Hajra; Umasish Jana.
J. Org. Chem., **65,** 6270- 6272 (2000).

43 Yun Ma; Changtao Qian; Limin Wang; Min Yang.
J. Org. Chem., **65,** 3864-3868 (2000).

44 Ch. Venkateshwar Reddy, M. Mahesh, P. V. K. Raju, T. Ramesh Babu and V. V. Narayana Reddy.
Tetrahedron Letters., **43(14),** 2657-2659 (2002). *Chem. Abstr.,* **137,** 169480 (2002).

45 Ranu C.; Alakananda Hajra;Suvendu S. Dey.
Organic Process Research and Development. **6(6),** 817-818 (2002).

46 Essa H. Hu; Daniel R. Sidler; Ulf H. Dolling.
J. Org. Chem. **63,** 3454-3457 (1998).

47 Flokers K.; Hrawood H. J.; Johnson T. B.
J. Am. Chem.Soc. **54,** 3751 (1932).

48 Kumar A. K.; Kastharian M.;Reddy C. S.; Reddy C. S.
Tetrahedron Letters. **42,** 7873-7875 (2001).

49 Ramalinga K.; Vijayalakshmi P.;Kaimal T. N. B.
Synlett., 863-865 (2001).

50 Yadav J. S.; Reddy B. V. S.; Srinavas R.; Venugopal C.; Ramalingam T.
*Synthesis.,*1341-1345 (2001).

51 Peng J.; Deng Y.
Tetrahedron Letters., **42,** 5917-5919 (2001).

52 Kappe C. O.; Kumar D.; Varma R.S.
Synthesis., 1799-1803 (1999).

53 Shingare M. S.;Madje B. R.; Shindalkar S. S.
Indian Journal of Heterocyclic Chemistry. **14,**179-180 (2004).

54 Narsaiah A. V.;Basak A. K.; Nagaiah.
Synthesis. **8,** 1253-1256 (2004).

55 Lu,J., Bai,Y.;
Synthesis, **4**, 466-470, (2002).

56 Jin, T., Zhang, S., Li, T.;
Synth Comm.; **32** (12), 1847-1851, (2002).

57 Lu,J., Bai, J.,Guo, Y.H., Wang, J., Ma, H.R.;
Chines J.Chem, **20**(7), 681-687, (2002).

58 Kidwai, M.,Saxena, S., Mohan, R., Venkataramanan, R.;
J.Chem.Soc. ;**1**, 16, 1845-1846, (2002).

59 Lu, J., Wang, F.L., Bai, Y.J., Li, W.H.,
Chines J. Chem., **22**(10), 788-792 (2002).

60 Varala, M., Alam, M.M., Adapa, S.R.;
Synlett.,**1**, 67-70 (2003).

61 Teimouri, F., Shaabani, A., Bazgir, A.;
Tetrahedron Lett., **44**(4), 857-859 (2003).

62 Martinez, S., Meseguer, M., Cases, L., Rodriguez, E., Molins, E., Vallribera, A.,
Tetrahedron, **59**(9), 1553-1556 (2003).

63 Sabitha, g., Reddy,G.S.K.K., Reddy, C.S., Yadav, J.S.;
Synlett, **6**, 858-860 (2003).

64 Xu, H., Wang, Y.H.,
Chinese, J.Chem., **21** (3), 327-331 (2003).

65 Salehi, H., Guo, Q.X.;
Synth. Comm., **34**(1), 171-179 (2004).

66 Yadav, J.S.,Reddy, B.V.S., Sridhar, P., Reddy, J.S.S., Nagaih, K., Lingaiah, K., Saiprasad, P.S.,
Eur. J.Org. Chem. ;**3**, 552-557, (2004).

67 Tu, S., Fang, F., Zhu, S., Li, T., Zhang, X., Zhuang,
Synlett, **3**, 537-539 (2004).

68 Zhidovinova, M.S., Fedorova, O.V., Rusinov, G.L., Ovachinnikova, I.G.;
Rusian.Chem.Bull.; **52** (11), 2527-2528 (2003).

69 Narsaiah,A.V., Basak, A.K., Nagaiah.;
Synthesis, **8**, 1253-1256 (2004).

70 Manjula, A., Rao, B.V., Neelakant,
Synth. Comm., **34** (14), 2665-2671 (2004).

71 Srinivas, K.V.N.S., Das, B.;
Synthesis, **13**, 2091-2093 (2004).

72 Reddy, Y.T., Rajitha, B., Reddy, P.N., Kumar, B.S.,Rao, V.P.;
Synthetic Communications, **34** (20), 3821-3825 (2004).

73 Bose, a., Padnekar,S., Ganguli, S., Chakraborty, G., Manhas, M.;
Tetrahedron Lett. **45**(45), 8351-8353 (2004).

74 O'Reilly B. C.; Atwal K. S.
Heterocycles., **26,**1185-1188 (1987).

75 Atwal K. S.; O'Reilly B. C.; Gougoutas J. Z.; Malley M. F.
Heterocycles., **26,** 1189-1192 (1987).

76 Atwal K. S.; Rovnyak G. C.; O'Reilly B. C.; Schwartz J.
J.Org. Chem., **54,** 5898-5907 (1989).

77 Ugi I.; Do¨ mling A.; Ho¨ rl, W.
Endeavour., **18,** 115-122 (1994).

78 Armstrong R. W.; Combs A. P.; Tempest P. A.; Brown S. D.; Keating T. A.
Acc. Chem. Res., **29,** 123-131 (1996)

79 Tietze L. F.; Lieb M. E.
Curr. Opin.Chem. Biol., **2,** 363-371 (1998).

80 Dax S. L.; McNally J. J.; Youngman M. A.

Curr. Med.Chem., **6,** 255-270 (1999).

81 Do¨ mling A.

Comb. Chem. High Throughput Screeni., **1,** 1-22 (1998).

82 Plunkett M.; Ellman J. A.

Combinatorial Chemistry and NewDrugs. Sci. Am., **276,** 68-73 (1997).

83 Schreiber S. L.

Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery Science., **287,** 1964-1969 (2000).

84 Weber L.; Illgen K.; Almstetter M.

Synlett., **3,**366-374 (1999).

85 Folkers K.; Johnson T. B.

J. Am. Chem.Soc., **55,** 3781-3791 (1933).

86 Folkers K.; Johnson T. B.

J. Am. Chem.Soc., **55,** 2886 (1933).

87 Kappe C. O.

Tetrahedron., **49,** 6937-6963 (1993).

88 Gallop M. A.; Barrett R. W.; Dower W. J.; Fodor S. P. A.; Gordon E. M.

J. Med. Chem. **37,** 1233, 1386 (1994).

89 Terrett N. K.; Gardner M.; Gordon D. W.;Kobylecki R. J.; Steele J.

Tetrahedron., **51,** 8135 (1995).

90 Thompson L. A.; Ellman J. A.

Chem.Rev., **96,** 555 (1996).

91 Gordon, E. M.; Gallop, M. A.; Patel, D. V.

Acc. Chem. Res., **29,** 144 (1996).

92 Rinnova M.; Lebl M.

Collect. Czech.Chem. Commun., **61,** 171 (1996).

93 Hermkens P. H. H.; Ottenheijm H. C. J.; Rees D.

Tetrahedron., **52,** 4527 (1996).

94 Fru¨ chtel J. S.; Jung G.

Angew. Chem., Int.Ed. Engl., **35,** 17 (1996).

95 Han H.; Wolfe M. M.; Brenner S.; Janda K. D.

Proc. Natl .Acad. Sci., U.S.A. **92,** 6419 (1984).

96 Han H.; Janda K. D.

J. Am. Chem.Soc., **118,** 2539, 7632 (1996).

97 Carell T.; Wintner E. A.; Bashir-Hashemi A.; Rebek J., Jr.
Angew. Chem., Int. Ed. Engl., **33,** 2059 (1994).

98 Carell T.; Wintner E. A.; Rebek J., Jr.
Angew. Chem., Int. Ed. Engl., **33,** 2061 (1994).

99 Carell T.; Wintner E. A.; Sutherland A. J.; Rebek J., Jr.; Dunayevskiy Y. M.; Vourous P.
Chem. Biol., **2,** 171 (1995).

100 Shipps, G. W., Jr.; Spitz U.P.; Rebek J., Jr.
Bioorg. Med. Chem., **4,** 655 (1996).

101 Cheng S.; Comer D. D.: Williams J. P.; Myers P. L.; Boger D. L.
J. Am. Chem. Soc., **118,** 2567 (1996).

102 Boger D. L.; Tarby C. M.; Myers P. L.; Caporale L. H.
J. Am. Chem. Soc., **118,** 2109 (1996).

103 Cheng S.; Tarby C. M.; Comer D. D.; Williams J. P.; Caporale L. H.; Myers P. L.; Boger D. L.
Bioorg.Med. Chem., **4,** 727 (1996).

104 Curran D. P. *Chemtracts.*
Org. Chem., **9,** 75 (1996).

105 Horva´ th, I. T.; Ra´ bai, J.
*Science.***266**, 72 (1994).

106 Zhu,D.W.
Synthesis., 953 (1993).

107 Gladysz J. A.
Science., **266,** 55 (1994).

108 Bergbreiter, D. E.
Chemtracts Org. Chem., **8,** 108 (1995).

109 Curran D. P.; Hadida S.
J. Am. Chem. Soc., **118,** 2531 (1993).

110 Curran D. P.; Hoshino M.
J. Org. Chem., **61,** 6480 (1996).

111 Hughes R. P.; Trujillo H. A.
Organometallics., **15,** 286 (1996).

112 DiMagno S. G.; Dussault P. H.; Schultz J. A.
J. Am. Chem. Soc. **118,** 5312 (1996).

113 Scott R. L.

J. Am. Chem. Soc., **70,** 4090 (1948).

114 Scott R. L.

J. Phys. Chem., **62,** 136 (1958).

115 Hildebrand J. H.; Cochran D. R. F.

J. Am. Chem. Soc., **71,** 22 (1949).

116 Hudlicky M.

Chemistry of Organic Fluorine Compounds; Ellis Horwood: Chichester, U.K., 1992.

117 Nefzi A.; Ostreh J. M.; Houghten R. A.

Chem. Rev., **97,** 449-472 (1997).

118 Corbett J. W. *A Review.*

Org. Prep. Proced. Int., **30,** 489-550 (1998).

119 Lewandowski K.; Murer P.; Svec F.; Fre´chet J. M.

Chem. Commun., 2237-2238 (1998).

120 Lewandowski K.; Murer P.; Svec, F.; Fre´chet J. M. J.

J. Comb. Chem., **1,** 105-112 (1999).

121 Wipf P.; Cunningham A.

Tetrahedron Lett., **36,** 7819-7822 (1995).

122 Hamaker L. K.; Yang K.; Drane J. A.; Peterson, M. L.

Proceedings of the Second LakeTahoe Symposium on Molecular Diversity, Tahoe City, January 19-24, (1998).

123 Garcia-Valverde M.; Pernat T.; Kappe C. O. Unpublished results.

124 Studer A.; Hadida S.; Ferritto R.; Kim S.-Y.; Jeger P.; Wipf P.

Science., **275,** 823-826 (1997).

125 Studer A.; Jeger P.; Wipf P.; Curran D. P.

J. Org. Chem., **62,** 2917-2924 (1997).

126 Atwal K. S.; Swanson B. N.; Unger S. E.; Floyd D. M.; Moreland S.; Hedberg A.; O'Reilly B. C.

J. Med. Chem., **34,** 806-811 (1991).

127 Rovnyak G. C.; Atwal K. S.; Hedberg A.; Kimball S. D.; Moreland S.; Gougoutas J. Z.; O'Reilly B. C.; Schwartz, J.; Malley, M. F.

J. Med. Chem., **35,** 3254-3263 (1992).

128 Grover G. J.; Dzwonczyk S.; McMullen D. M.; Normandin D. E.; Parham C. S.; Sleph P. G.; Moreland, S.

J. Cardiovasc. Pharmacol., **26,** 289-294 (1995).

129 Nagarathnam D.; Miao S. W.; Lagu B.; Chiu G.; Fang J.; Dhar T. G. M.; Zhang J.; Tyagarajan S.; Marzabadi M. R.; Zhang F. Q.; Wong W. C.; Sun W. Y.; Tian D.; Wetzel J. *J. Med. Chem.,* **42,** 4764-4777 (1999).

130 Barrow, J. C.; Nantermet P. G.; Selnick H. G.; Glass K. L.; Rittle K. E.; Gilbert K. F.; Steele T. G.; Homnick C, F.; Freidinger R. M.; Ransom R. W.; Kling P.; Reiss, D. *J. Med. Chem.,* **43,** 2703-2718 (2000).

131 Rovnyak G. C.; Kimball S. D.; Beyer B.; Cucinotta G.; DiMarco J. D.; Gougoutas J.; Hedberg A.; Malley M.; McCarthy J. P.; Zhang R.; Moreland S. *J. Med. Chem.,* **38,** 119-129 (1995).

132 Kleidernigg O. P.; Kappe C. O. *Tetrahedron Asymmetry,* **8,** 2057-2067 (1997).

133 Kappe C. O. *Acc. Chem Res.,* **33,** 879-888 (2000).

134 Wang F.; Loughlin T.; Dowling T.; Bicker G.; Wyvratt J. *J. Chromatogr.,* **872,** 279-288 (2000).

135 Schnell B.; Strauss U. T.; Verdino P.; Faber, K.; Kappe C. O. *Tetrahedron Asymmetry,* **11,** 1449-1453 (2000).

136 Krenn W.; Verdino P.; Uray G.; Faber K.; Kappe C. O. *Chirality,* **11,** 659-662 (1999).

137 Kappe C. O.; Shishkin O. V.; Uray G.; Verdino P. *Tetrahedron,* **56,** 1859-1862 (2000).

138 Elliott M. C.; Monk A. E.; Kruiswijk E.; Hibbs D. E.; Jenkins R. L.; Jones D. V. *Synlett.,* 1379-1382 (1999).

139 Elliot M. C.; Kruiswijk E.; Willock D. J. *Tetrahedron Lett.,* **39,** 8911-8914 (1998).

140 Kappe C. O.; Uray G.; Roschger P.; Lindner W.; Kratky C.; Keller W. *Tetrahedron,* **48,** 5473-5480 (1992).

141 Valpuestra Ferna´ndez M.; Lo´ pez Herrera F. J.; Lupio´n Cobos T. *Heterocycles,* **27,** 2133-2140 (1988).

142 Heys L.; Moore C. G.; Murphy P. J. *Chem. Soc. Rev.,* **29,** 57-67 (2000).

143 McDonald A. I.; Overman L. E. *J. Org. Chem.,* **64,** 1520-1528 (1999)

144 Franklin A. S.; Ly S. K.; Mackin G. H.; Overman L. E.; Shaka A.

J. Org.Chem., **64,** 1512-1519 (1999).

145 Cohen F.; Overman L. E.; Ly Sakata S. K.
Org. Lett., **1,** 2169-2172 (1999).

146 Overman L. E.; Rabinowitz M. H.; Renhowe P. A. A.
J. Am. Chem. Soc. **117,** 2657-2658 (1995).

147 Coffey D. S.; McDonald A. I.; Overman L. E.; Stappenbeck F.
J. Am. Chem. Soc., **121,** 6944-6945 (1999).

148 Coffey D. S.; Overman L. E.; Stappenbeck F
J. Am. Chem. Soc., **122,** 4904-4914 (2000).

149 Coffey D. S.; McDonald A. I.; Overman L. E.; Rabinowitz M. H.; Renhowe P. A.
J. Am. Chem. Soc., **122,** 4893-4903 (2000).

150 Kappe C. O.; Falsone S. F.
Synlett., 718-720 (1998).

151 Patil A. D.; Kumar N. V.; Kokke W. C.; Bean M. F.; Freyer A. J.; De Brosse C.; Mai S.; Truneh A.; Faulkner D. J.; Carte B.; Breen A. L.; Hertzberg R. P.; Johnson R. K.; Westley
J. Org. Chem., **60,** 1182-1188 (1995).

152 Hong C. Y.; Kishi Y.
J. Am. Chem. Soc., **114,** 7001-7006 (1992).

153 Taguchi H.; Yazawa H.; Arnett J. F.; Kishi Y.
Tetrahedron Lett., 627-630 (1977).

154 *J. Am. Chem. Soc.,* **99,** 2818-2119 (1977).

155 Kishi Y.
Heterocycles, **14,** 1477-1495 (1980).

156 Sweet F. S.; Fissekis J. D.
J. Am.Chem. Soc., **95,** 8741-8749 (1973).

157 Kappe C. O.
J. Org. Chem., **62,** 7201-7204 (1997).

158 Folkers K.; Johnson T. B.
J. Am. Chem. Soc., **55,** 3784-3791 (1933).

159 Sweet F.; Fissekis J. D.
J. Am. Chem. Soc., **95,** 8741-8749 (1973).

160 Folkers K.; Harwood H. J.; Johnson T. B.
J. Am. Chem. Soc. **54,** 3751-3758 (1932).

161 Nielson A. T.; Houlihan W.

Org. React. (N.Y.), **16,** 1-438 (1968).

162 Folkers K.; Johnson T. B.
J. Am. Chem. Soc., **55,** 2886-2893 (1933).

163 Heathcock C. H.; Trost B.M.; Fleming I.
Comprehensive Organic Synthesis, **2,**133-179 (1991).

164 Donleavy J. J.; Kise M. A.
Org. Synth., **2,** 422-423 (1943).

165 Senda S.; Suzui A.
Chem. Pharm.Bull., **6,** 476-479 (1958).

166 Hlousek J.; Machacek V.; Sterba V.
Sb. Ved. Pr., Vys. Sk. Chemickotechnol. Pardubice, **39,** 11-25 (1978).
C*hm. Abstr.,* **91,** 174663*n* (1979).

167 Kappe C. O.; Roschger P.
J. Heterocycl. Chem., **26,** 55-64 (1989).

168 Schiff H.
Ann. 151, 186-213 (1869).

169 Bakibaev A. A.; Tignibidina L. G.; Filimonov V. D.; Gorshkova V. K.; Saratikov A. S.
Khim. Farm. Zh., **25,** 31-35 (1991).

170 Bakibaev, A. A.
Zh. Org. Khim., **11,** 1686-1687 (1994).

171 Schiff H.
Ann., **291,** 367-377 (1896).

172 Koyano, K.; McArthur C. R. *Can.*
J. Chem., **51,** 333-337 (1973).

173 Overman L. E.; Ricca D. J. Trost B. M.; Fleming, I.
Comprehensive Organic Synthesis, **2,** 1007-1046 (1991).

174 Hiemstra H.; Speckamp W. N.; Trost B. M.; Fleming I.
Comprehensive Organic Synthesis, **2,** 1047-1082 (1991).

175 Okamoto K. T.; Clardy J.
Tetrahedron Lett., **25,** 2937-2940 (1984).

176 Dijkink J.; Deghati P. Y. F.; Hiemstra H.
11th IUPAC Conference on Organic Synthesis, Amsterdam, June 30-July 4, 1996,
Book of Abstracts p 379.

177 Kretsinger R. H.

Adv. Cyclic Nucleotide Res., **11,** 1 (1979).

178 Rosenberger L. B.; Triggle D. J.
Calcium and Drug Action; G. B. Weiss, Ed.; Plenum Press: New York, 1978.

179 Putney Jr., J. W.
Pharmacol. Rev., **30,** 209 (1978).

180 Triggle D. J.
New Perspectives on Calcium Antagonists; G. B. Weiss, Ed.; American Physiological Society: Bethesda, MD 1981.

181 Fleckenstein A. Annu.
Rev. Pharmacol. Toxicol, **17,** 149 (1977).

182 Cho H.; Ueda M.; Shima K.; Mizuno A.; Hayashimatsu M.; Ohnaka Y.; Takeuchi Y.; Hamaguchi M.; Aisaka K.; Hidaka T.; Kawai M.; Takeda M.; Ishihara T.; Funahashi K.
J. Med. Chem., **32,** 2399 (1989).

183 Atwal K.; Rovnyak G. C.; Schwartz J.; Moreland S.; Hedberg A.; Gougoutas J.Z.; Malley M. F.; Floyd D. M.
J. Med. Chem., **33,** 1510 (1990).

184 Atwal K. S.; Rovnyak G. C.; Kimball S. D.; Floyd D. M.; Moreland S.; SwansonB. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F.
J.Med. Chem., **33,** 2629 (1990).

185 Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O´Reilly, B. C.
J. Med. Chem., **34,** 806 (1991).

186 Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J.
J. Cardiovasc. Pharmacol, **26,** 289 (1995).

187 Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg,A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S.
J. Med. Chem., **38,** 119 (1995);

188 Triggle, D. J.; Padmanabhan, S.
Chemtracts Org. Chem., **8,** 191 (1995).

189 Review: Goldman, S.; Stoltefuss, J.
Angew. Chem., Int. Ed. Engl., **103,** 1587 (1991).

190 Schleifer, K. J.
J. Med. Chem., **42,** 2204 (1999).

191 Striessnig, J.; Grabner, M.; Mitterdorfer, J.; Hering, S.; Sinnegger, M.; Glossmann, H. *Trends Pharmacol. Sci.,* **19,** 108 (1998).

192 Kappe C. O.; Birgit J.; Tetiana P. *Molecules,* **5,** 227-239 (2000).

193 Ondetti, M. A.; Rubin, B.; Cuahman, D. W. *Science,* **196,** 441-444 (1977).

194 Martin, P.; Bachmann, B.; Ganten, D. *Trends Cardiovas. Med.,* **2,** 94-99 (1992).

195 Corveol, P. *Theory Prac.,* AII (Suppl. 2) 463-470 (1989).

196 Hollenberg, N. K. *Annu. Rev. Pharmacol. Toxicol.,* **19,** 559-581 (1979).

197 Geenlee, W. *J. Med. Res. Rev.,* **10,** 174-236 (1990).

198 Pals, D. T.; Denning, G. S., Jr.; Keenan, R. E. *Historical Development of Saralasin.,* 15 (Suppl. 9), S7-10. (1979).

199 Atwal K. S.;Ahmed S. Z.; Eileen B. B.; Delaney C. L.; Dickinson K. E.; Francis N.F.; Aners H.; Miller A. V.; Suzanne Moreland, Brian C. O'Reilly, Thomas R. Schaeffer, *J. Med. Chem.,* **35,** 4751-4763 (1992).

200 Dhanapalan N.; Shou Wu M.; Bharat L.; George C.; James F.; Murali T. G.; Jack Z.; Sriram T.; Mohammad R. M.; Fengq Z.; Wai C. W.; Wanying S.; Dake T.; John M. W. *J. Med. Chem.,* **2,** 4764-4777 (1999).

201 Murali T. G.; Dhanapalan N.; Mohammad R. M.; Bharat L.; Wai C. W.; George C.; Sriram T.; Shou Wu M.; Fengqi Z.; Wanying S.; Dake T.; Quanrong S.; Jack Z.; John M. W. *J. Med. Chem.,* **42,** 4778-4793 (1999).

202 Bharat Lagu, Dake Tian, Dhanapalan Nagarathnam, Mohammad R. Marzabadi, Wai C. Wong,Shou W. Miao, Fengqi Zhang, Wanying Sun, George Chiu, James Fang. *J. Med. Chem.,* **42,** 4794-4803 (1999).

203 James C. Barrow, Philippe G. Nantermet, Harold G. Selnick, Kristen L. Glass, Kenneth E. Rittle, Kevin F. Gilbert, Thomas G. Steele, Carl F. Homnick, Roger M. Freidinger. *J. Med. Chem.,* **43,** 2703-2718 (2000).

204 Frederick Cohen, Larry E. Overman, Sylvie K. Ly Sakata. *Organic Letters,* **1(13),** 2169-2172 (1999).

205 Patil, A. D.; Kumar, N. V.; Kokke, W. C.; Bean, M. F.; Freyer, A. J.; Debrosse, C.; Mai, S.; Truneh, A.; Faulkner, D. J.; Carte, B.; Breen, A. L.; Hertzberg, R. P.; Johnson, R. K. *J.Org. Chem.,* **60,** 1182-1188 (1995).

206 Patil, A. D.; Freyer, A. J.; Taylor, P. B.; Carte, B.; Zuber, G.; Johnson, R. K.; Faulkner, D. J.
J. Org. Chem., **62,** 1814-1819 (1997).

207 Snider, B. B.; Chen, J.; Patil, A. D.; Freyer, A. J.
Tetrahedron Lett., **37,** 6977-6980 (1996).

208 Gomes, R.; Berlinck, S.
Prog. Chem. Org. Nat. Prod., **66,** 119 (1995)

209 Berlinck, R. G. S.
Nat. Prod. Rep., 377 (1996).

210 Greenhill, J. V.; Pharm, B.; Lue, P.
Prog. Med. Chem., **30,** 203 (1993).

211 Sweet, R. W.; Truneh, A.; Hendrickson, W. A.
Cum. Opin.Biotech., **2,** 622-633 (1991).

212 Ryu, *S.* E.; Kwong, P. D.; Truneh, A.; Porter, T G.; Arthos, J.; Rosenberg, M.; Dai, X.; Xuong, N.; Axel, R.; Sweet, R. W.; Hendrickson, W. A.
Nature., **348,** 418-426 (1991).

213 Culp J. S.; Johansen H.; Hellmig, B.; Beck J.; Matthews T. .; Delers A.; Rosenberg M.
BiolTechnology., **9,** 173-177 (1991).

214 Dean, K. C.; MacDougal, J. S.; Inacker, R.; Folena-Wasserman, G.; Arthos, J.; Rosenberg, J.; Maddon, T J.; Axel, R.; Sweet, R. W.
Nature., **331,** 82-84 (1988).

215 Faulkner, D. J.
Nat. Prod. Rep., **15,** 113-158 (1998).

216 Jares-Erijman, E. A.; Sakai, R.; Rinehart, K. L.
J. Org. Chem. **56,** 5712-5715 (1991).

217 Tavares, R.; Daloze, D.; Braekman, J. C.; Hajdu, E.; Muricy, G.; Van Soest, R. W. M.
Biochem. Syst. Ecol., **22,** 645-646 (1994).

218 Berlinck, R. G. S.; Braekman, J. C.; Daloze, D.; Bruno, I.; Riccio, R.; Ferri, S.; Spampinato, S.; Speroni, E.
J. Nat. Prod., **56,** 1007-1015 (1993).

219 Kashman, Y.; Hirsh, S.; McConnell, O. J.; Ohtani, I.; Kusumi, T.; Kakisawa, H.

J. Am. Chem. Soc., **111,** 8925-8926 (1989).

220 Ohtani, I.; Kusumi, T.; Kakisawa, H.; Kashman, Y.; Hirsh, S.
J. Am. Chem. Soc., **114,** 8472-8479 (1992).

221 Ohtani, I.; Kusumi, T.; Kakisawa, H.
Tetrahedron Lett., **33,** 2525-2528 (1992).

222 Synthetic ptilomycalin A (NSC 700559) exhibits mid-nanomolar activity against many tumors in the NCI in vitro panel, with particular selectivity realized against non-small cell lung cancer (HOP-62) and melanoma (M14).

223 Jares-Erijman, E. A.; Ingrum, A. L.; Carney, J. R.; Rinehart, K. L.; Sakai, R.
J. Org. Chem., **58,** 4805-4808 (1993).

224 Duschinsky, R.; Gabriel, T.; Tautz, W.; Nussbaum, A. W.; Hoffer, M.; Grunberg, E.
J. Med. Chem., **10,** 47 (1967).

225 Bernardinelli, G.; Benhamza, R.; Tronchet, J. M.
J. Acta.Cryst., **C45,** 1917 (1989).

226 Chang, C.; Roth, B.
Some Pyrimidines of Biological and Medicinal Interest—II, Progress in Medical Chemistry; Butterworths:
London, **7,** 311 (1970).

227 Samuel, A. G.; Mereyala, H. B.; Ganesh, K. N.
Nucleosides Nucleotides, **11,** 49 (1992).

228 Fouque, B.; Teoule, R.
Chemotherapy., **20,** 221 (1974).

229 Cheraghali, A. M.; Kumar, R.; Wang, L.; Knaus, E. E.; Wiebe, L. I.
Biochem. Pharmacol, **47,** 1615 (1994).

230 Kumar, R.; Wiebe, L. I.; Knaus, E. E.
Arch. Pharm., **330,** 259 (1997).

231 Kumar, R.; Wang, L.; Wiebe, L. I.; Knaus, E. E.
Nucleosides Nucleotides, **15,** 265 (1996).

232 Kumar, R.; Wang, L.; Wiebe, L. I.; Knaus, E. E.
J. Med. Chem., **37,** 4297 (1994).

233 Kumar, R.; Wiebe, L. I.; Knaus, E. E.
Can. J. Chem., **72,** 2005 (1994).

234 Kumar, R.; Wang, L.; Wiebe, L. I.; Knaus, E. E.
J. Med. Chem., **37,** 3554 (1994).

235 Kumar, R.
Bioorganic & Medicinal Chemistry Letters, **12,** 275–278 (2002).

236 Andrew L. Hopkins, Jingshan Ren, Robert M. Esnouf, Benjamin E. Willcox, E. Yvonne Jones, Carl Ross, Tadashi Miyasaka, Richard T. Walker, Hiromichi Tanaka, David K.
J. Med. Chem., **39,** 1589-1600 (1996).

237 Baba, M.; Tanaka, H.; De Clercq, E.; Pauwels, R.; Balzarini, J.; Schols, D.; Nakashima, H.; Perno, C. F.; Walker, R. T.; Miyasaka,T.
Biochem. Biophys. Res. Commun., **165,** 1375-1381 (1989).

238 Baba, M.; De Clercq, E.; Tanaka, H.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Umezu, K.; Nakashima, H.; Mori, S.; Shigeta, S.; Walker, R. T.; Miyasaka, T.
Proc. Natl. Acad. Sci., U.S.A. **88,** 2356-2360 (1991).

239 Baba, M.; De Clercq, E.; Tanaka, H.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Umezu, K.; Walker, R. T.; Mori, S.; Ito, M.; Shigeta, S.; Miyasaka, T.
Mol. Pharmacol, **39,** 805-810 (1991).

240 Tanaka, H.; Baba, M.; Hayakawa, H.; Sakamaki, T.; Miyasaka, T.; Ubasawa, M.; Takashima, H.; Sekiya, K.; Nitta, I.; Shigeta, S.; Walker, R. T.; Balzarini, J.; De Clercq,
J. Med. Chem., **34,** 349-357 (1991).

241 Baba, M.; Shigeta, S.; Tanaka, H.; Miyasaka, T.; Ubasawa, M.; Umezu, K.; Walker, R. T.; Pauwels, R.; De Clercq, E.
Antiviral Res., **17,** 245-264 (1992).

242 Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R. T.; Balzarini, J.; De Clercq, E.
J. Med. Chem., **32,** 2507-2509 (1989).

243 Yuasa, S.; Sadakata, Y.; Takashima, H.; Sekiya, K.; Inouye, N.; Ubasawa, M.; Baba, M.
Mol. Pharmacol, **44,** 895-900 (1993).

244 Baba, M.; Shigeta, S.; Yuasa, S.; Takashima, H.; Sehiya, K.; Ubasawa, M.; Tanaka, H.; Miyasaka, T.; Walker, R. T.; De Clercq, E.
Antimicrob. Agents Chemother, **38,** 688-692 (1994).

245 Balzarini, J.; Karlsson, A.; De Clercq, E.
Mol. Pharmacol, **44,** 694-701 (1993).

246 Victor E. Marquez, Abdallah Ezzitouni, Pamela Russ, Maqbool A. Siddiqui,Harry Ford, Jr. Ron J. Feldman, Hiroaki Mitsuya, Clifford George, Joseph J. Barchi, Jr.
J. Am. Chem. Soc., **120,** 2780-2789 (1998).

247 *Drug Data Report*; **8**(1), 35 (1986).

248 *Drug Data Report,* **10**(3), 200 (1988).

249 *Drug Data Report,* **24**(2), 165, (2002).

250 *Drug Data Report,* **8**(5), 465 (1986).

251 *Drug Data Report,***10**(10), 826 (1988).

252 *Drug Data Report,***10** (11), 899 (1988).

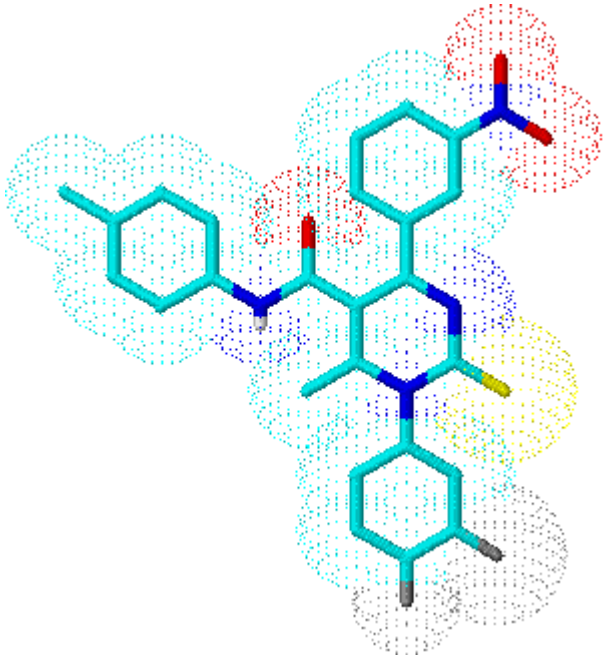
253 Clin Microbiol Infect **9,** 1504 (2003).

254 Lancet. **361** (9357), 577 (2003).

255 V. M. Parikh;
Absorption spectroscopy of organic molecules, Addition-Wesley Pub. Co. London 243, 258 (1978). A. Hand book of spectroscopic data by B. D. Mishtry; 1st ed. ABD Press Jaipur 11-36 (2000).

256 A. R. Kartizky and R. Alans Jones;
J. Chem. Soc., 2942 (1960). Introduction of Infra fed and Raman spectroscopy by Norman B. Colthup, Lowrence H. Daly and Stephan E. Wiberluy. Academic Press (1975).

257 A. L. Barry;
The antimicrobial susceptibility test: Principle and practices, edited by *llluslea & Febiger*, *(Philadelphia), USA*, 180; *Biol. Abstr.*, **64**, 25183 (1977).



PART - II

STUDIES ON

DIHYDROPYRIMIDINTHIONES

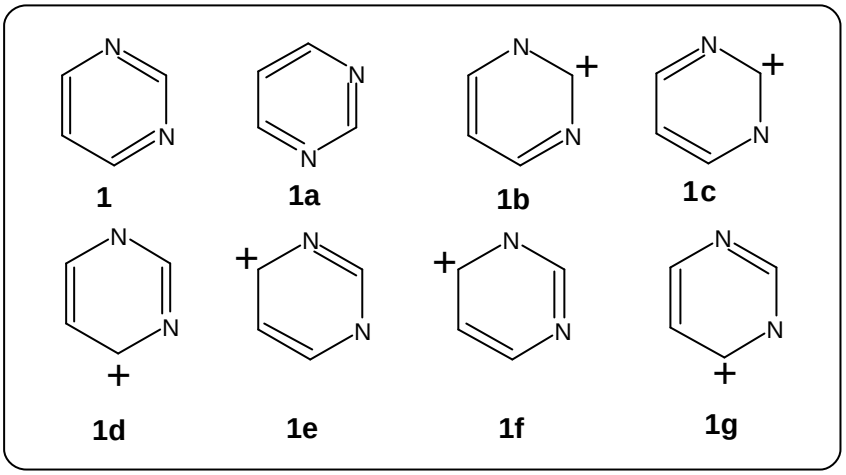
INTRODUCTION

Thiourea itself was one of the first new drug employed to depress, the clinically over active thyroid in thyrotoxicosis[1] but some of the cyclic thioureides have been found better suited. All of these are prone of produce adverse reduction in susceptible patients and found more potent and less likely to produce side effect and is being used widely.[2]

Generally pyrimidine derivatives such as 2-hydroxy pyrimidine, 2-mercapto pyrimidine and 2-amino pyrimidine are studied. Pyrimidines have been isolated from the hydrolysis of the nucleic acid.

Pyrimidines are among those molecules that make life possible, have been some of the building blocks of DNA and RNA. Several analogs of pyrimidines have been used as compounds that interfere with the synthesis and functioning of nucleic acids e.g. fluorouracil, which has been used in cancer treatment. Also there are some thiouracil derivatives, which produce adverse reduction in susceptible patients and found more potent and less likely to produce side effects and is being widely used. There are several other important groups of pyrimidines with medicinal uses.

Pyrimidine ring carrying various subtituents may be built up from two or three aliphatic fragments by the principle synthesis or by a variety of other synthesis, which are complimentary rather than alternative to it. A second type of synthesis is the isomerisation or break down of another heterocycles such as an hydration of purine but such roots are frequently used. Pyrimidine is best considered as a resonance hybrid to which the uncharged equivalent Kekule structures **1** and **1a** and charged structures **1** and **1a** and charged structures **1b** and **1g** contribute. The self consistent p (pi) electron densities required for the ground state of pyrimidine are 0.776, 0.825 and 1.103 for positions 2, 4 and 5 respectively. Despite considerable localization of p (pi) electrons at nitrogen atoms of pyrimidines, the ring system is still sufficiently aromatic to possess substantial stability. This is great advantage in the primary synthesis of pyrimidines.

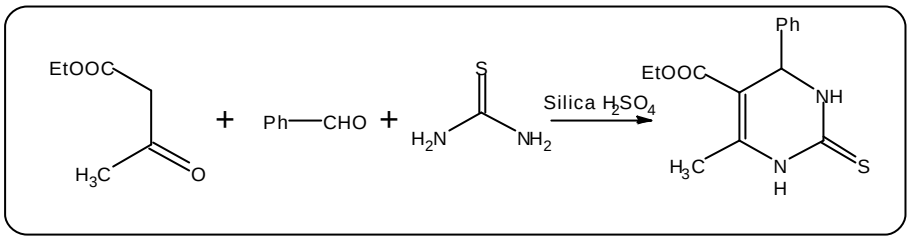


From the theoretical view point, it is essential to predict the structure, binding properties, chemical reactivity, etc. of dihydro compounds from the number and positioning of nitrogen atoms in the ring, as well as from the disposition of double bonds. Such quantum mechanical calculations also enable an evaluation of the degree of aromatic character in potential "homoaromatic" and "antiaromatic" isomers. Availability of novel model compounds for verifying these predictions would open up new horizons in theoretical heterocyclic chemistry, particularly in clarifying the structures leading to spontaneous isomerization of a derivative or in verifying its redox properties.

From the biochemical point of view, 1,4-dihydropyrimidine are of intense interest because of presence of this group at the active site of the "hydrogen transferring coenzyme" NADH (reduced nicotinamide adenine dinucleotide). This nucleotide, a central participant in metabolic processes in living organisms, participates in the reduction of various unsaturated functionalities.

SYNTHETIC ASPECT :-

(1) Silica Sulfuric acid efficiently catalyzes the three component Biginelli reaction between an aldehyde, a β-cabonyl compound, and thiourea in ethanol to afford the corresponding dihydropyrimidines in high yield.[3] The catalyst is reusable and can be applied several times without any decrease in the yield of the reaction.

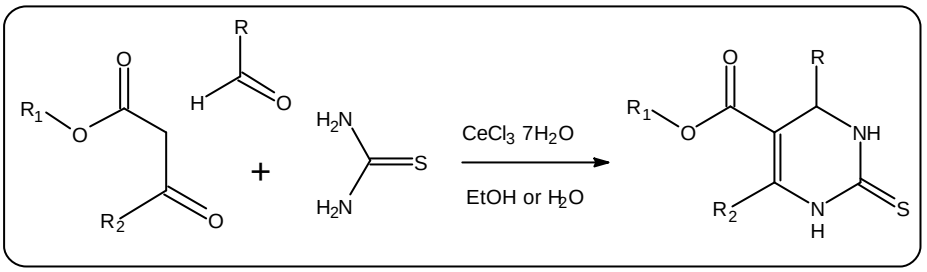


(2) Some Biginelli compounds were synthesized by using a photochemistry method. The Biginelli three component cyclocondensation reaction in THF medium using a mixture of β-ketoester or β-diketone, aryl aldehyde and thiourea under irradiation with a tungstan lamp light to gave DHPM-2-(1H)-thiones.[4]

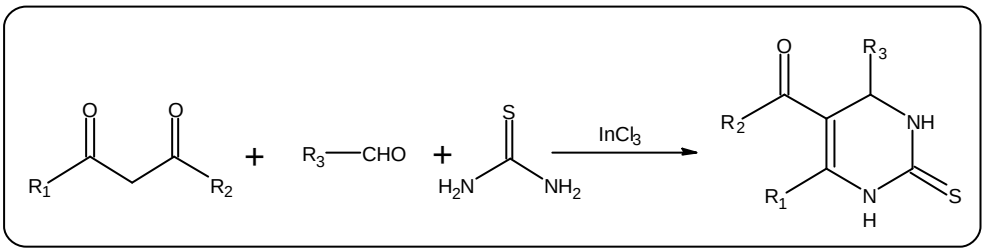
(3) DHPM was prepared from three component β-diketone, aldehyde and thiourea coupling in ethanol catalyze by indium(III) tribromide(In Br_3).[5,6] This modified one-pot Biginelli condensation provided not only simple preparation but also this modified Biginelli reaction was oxygen-bridge.

(4) Subhas D. Bose et al. [7] describe a general and practical route for the Biginelli cyclocondensation reaction using cerium(III) chloride ($CeCl_3$) heptahydrate as the catalyst. Three different sets of reaction conditions were examined (I) traditional ethanol reflux (ii) water reflux and (iii) solvent-free conditions. This is a novel, one-pot combination that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produces excellent yields

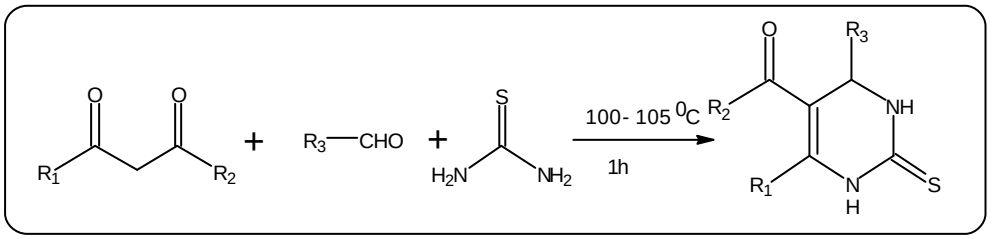
of the DHPM-2(1H)-thiones.



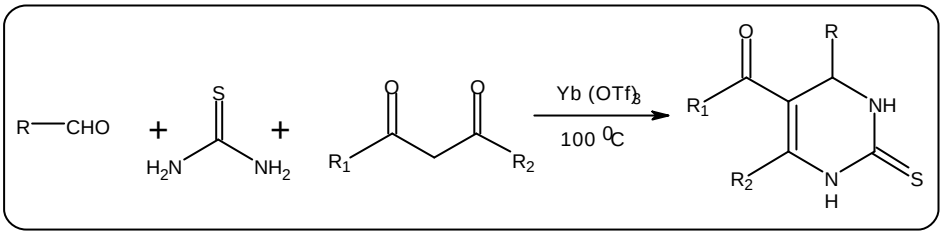
(5) Recently, Indium(III) chloride was emerged as a powerful Lewis catalyst imparting high region and chemo selectivity in various chemical transformations. Ranu C.et al.[8] described a simple synthesis of DHPM-2-(1H)-thione derivatives, using indium(III) chloride (10 mol %) as a catalyst from an aldehyde, β-dicarbonbyl compound and thiourea in THF.



(6) A practical and green chemistry approach towards synthesis of DHPM-2-(1H)-thione without any solvent or catalyst. This method was developed by Ranu C. et al.[9] Title compound was prepared from three component β-diketone, aldehyde and thiourea was heated under stirring at 100-105 ^{0}C afford the corresponding DHPM-2-(1H)-thione in high yield (82%) and purity (> 95%).

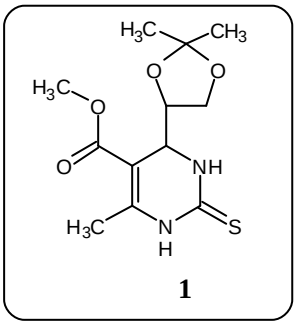


(7) Recently, Wang L. et al.[10-12] developed novel one pot Biginelli-type reaction. Aromatic and aliphatic aldehydes with β-dicarbonbyl compound and thiourea in presence of catalytic amount of 5 % of $Yb(OTf)_3$ at 100 ^{0}C for 60-90 minute under solvent free condition proceeded smoothly to afford the corresponding DHPM thione.



Structural Variation Of Reactoin :-

The original cyclocondensation reaction has been extended widely to include variation in all three components. If these, the aldehydes component has been varied to the largest extent and now includes not only many aromatic[13-27] but also aliphatic[14,15,22,28-31] and heterocyclic aldehydes[14,22,29,32-35] can also be used. Particular interest are reaction where the aldehydes component is derived from a carbohydrate. In such reaction dihydropyrimidines having a sugar-like moiety at position four (C-nucleoside analogs) i.e. **(1) or (2)** are obtained.



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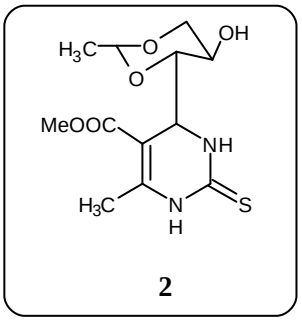
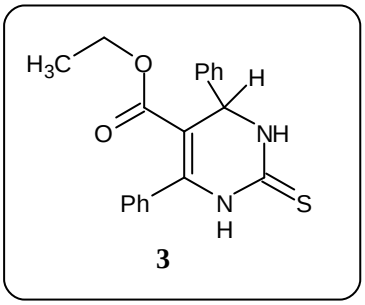


2

Apart from common alkyl acetoacetates which are employed frequently as the β-ketoester components, other acetoacetic acid such as benzyl acetoacetate,[28,36]

(-)-methyl acetoacetate,[36] β-chloroethyl acetoacetate,[37] 2-furanylmethyl acetoacetate,[38] and ethylthio acetoacetate[38] have been used successfully in the Biginelli reaction; benzoylacetic acid esters react analogously to form **(3)**.[28] Similarly, ethyl 4-bromo acetoacetate,[34] and ethyl trifluoromethyl acetoacetate[16] afford the corresponding 6-functionalized dihydropyrimidines **(4)**.



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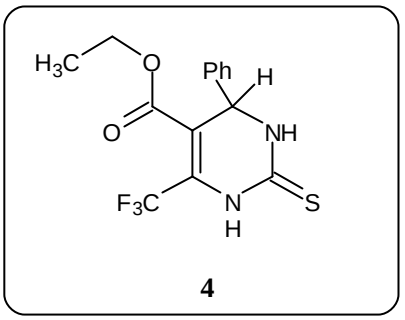
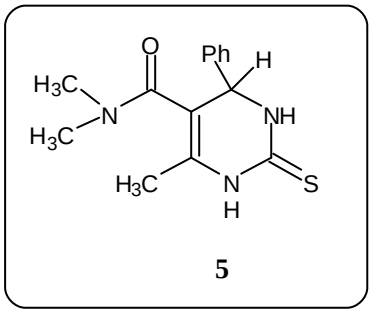


4

Primary, secondary and tertiary acetoacetamides have been used in place of ester to produce pyrimidine-5-carboxamides **(5).**[17,27,39-42] It should be emphasized that monosubstituted thioureas from exclusively N-1 substituted dihydropyrimidines of type **(6)**.[14,19,28,29,33,38,40,42-46]



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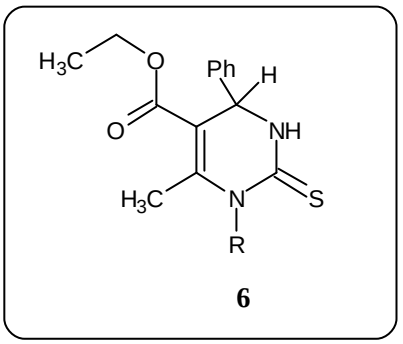
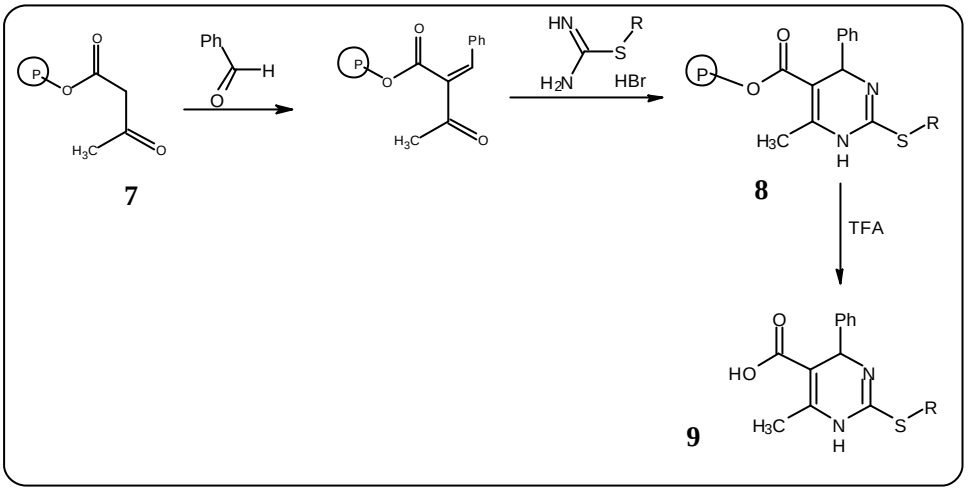


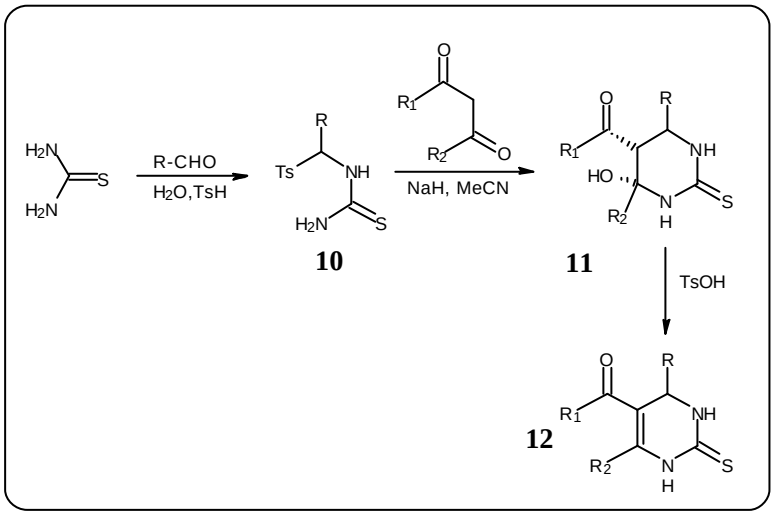
6

In addition to solid-phase adaptions of the traditional three-component Biginelli condensation, solid-phase variations of the "Atwal modification" of the Biginelli reaction have also been reported. Robinett et al.[47] have disclosed the synthesis of a 648-member combinatorial library of 1,4-dihydropyrimidines **(9)**. Towards this end, polymer-bound acetoacetate **(7)** was subjected to Knoevenagel condensation with aromatic aldehydes, followed by condensation with isothioureas.

The resulting polymer-bound 1,4-dihydropyrimidines **(8)** were cleaved from the resin with 50% TFA to produce carboxylic acid **(9)**.

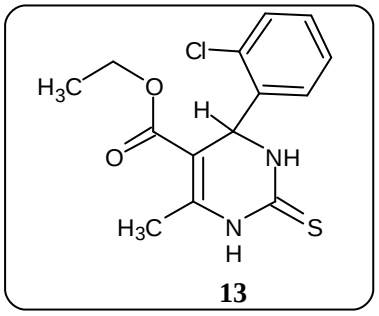


One other novel approach to DHPMs has been described by Shutalev et al.[48] is outlined below. This synthesis is based on the condensation of readily available R-tosyl-substituted thioureas **(10)** with the (in situ prepared) enolates of acetoacetates or 1,3-dicarbonyl compounds. The resulting hexahydropyrimidines **(11)** need not to be isolated and can be converted directly into DHPMs **(12)**. This method works particularly well for aliphatic aldehydes and thioureas and produces high overall yields of the desired target compounds.



Therapeutic Importants :

Biginelli compound show a diverse range of biological activities. As early as 1930 simple derivatives **(13)** were patented as agent for the protection of wool against moths.[49] Later, interest focused on the antiviral activity of Biginelli compounds.[50]



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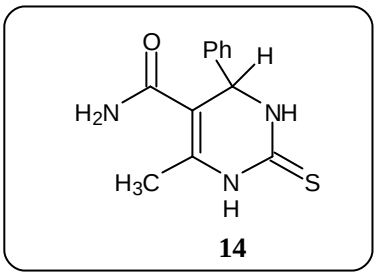
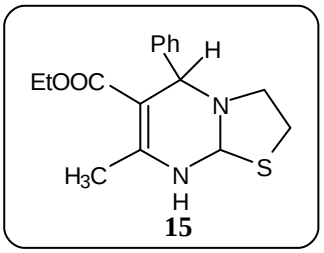


14

Pyrimidine-5-carboxamides derivatives of type **(14)** were reported to possess anticarcinogencic activity, [51] antiinflammaroty, [27,52] analgesic [27] and blood platelet aggregation inhibitory activity.[24]

The main interest in Biginelli compounds, however, is due to the strong antihypertensive activity exhibited by certain derivatives. This is not surprising, since these dihydropyrimidines can be regarded as aza-analogs of dihydropyridines of the nifedipine type. Dihydropyridines have found widespread use in cardiovascular medicine and have served as important tools for the study of calcium channel structure and function.[53]

Simple modificatios of the aromatic ring are reported to give substances with only moderate cardiovascular activity, e.g. **(13)**, [25] **(16)**, [19,54,55] **(17)** were shown to be potent calcium channel blockers, [56-58] but they do not shown any significant antihypertensive activity *in vivo*. [56] This is also the case for bicyclic dihydropyrimidines **(15)**. [59,60]



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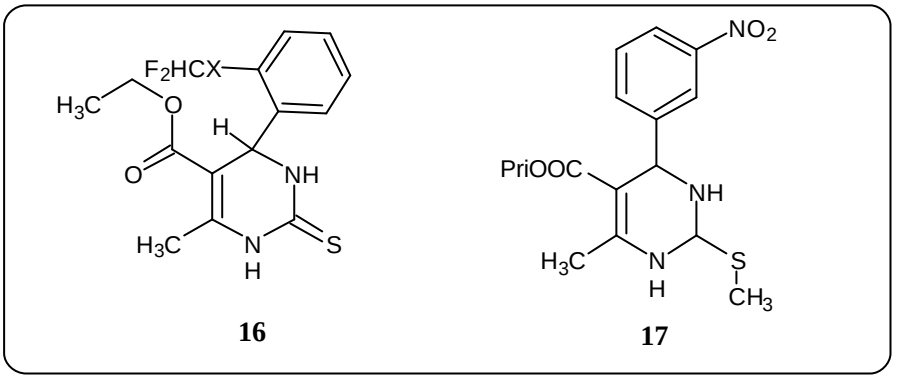
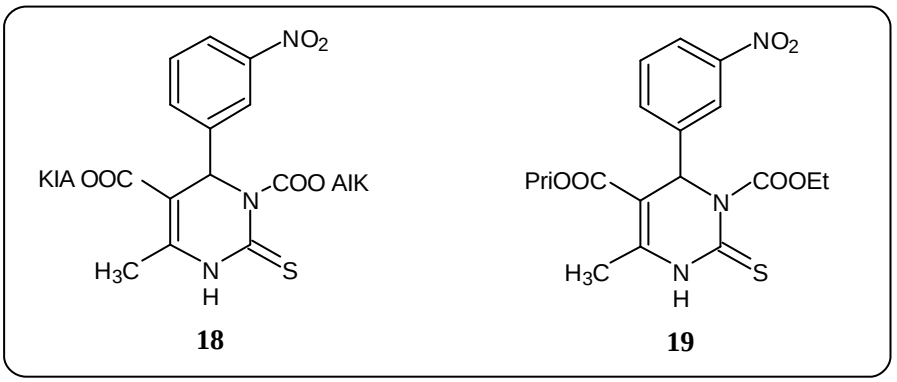


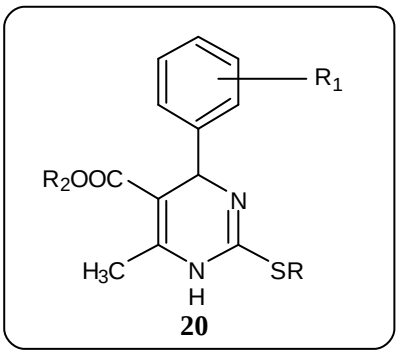
16 **17**

Among the most potent derivatives are Biginelli compounds bearing an ester group at N-3 **(18)**, thereby closely resembling the nifedipine structure.[61-64] Although the calcium channel blocking activity of these compounds, e.g**(19)**, is comparable to dihydropyridines, most of them are devoid of antihypertensive activity*in vivo*.[62]



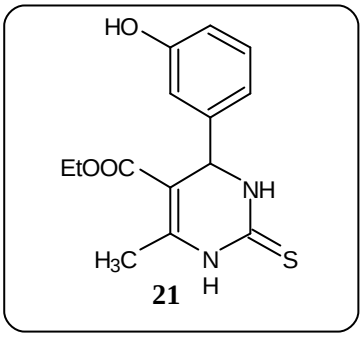
18 **19**

Atwal K. S. et al.[65] synthesized the 2-[[(4-methoxyphenyl)methyl]thio]-dihydropyrimidine **(20)** and investigated that pyrimidines are integral parts of such biologically important compounds as antiviral,[66,67] antitumor [68] and cardiovascular agent.[69]



20

A very recent highlight in this context has been the identification of the structurally rather simple DHPM monastrol **(21)** as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest.[70] Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drugs.[70,71]

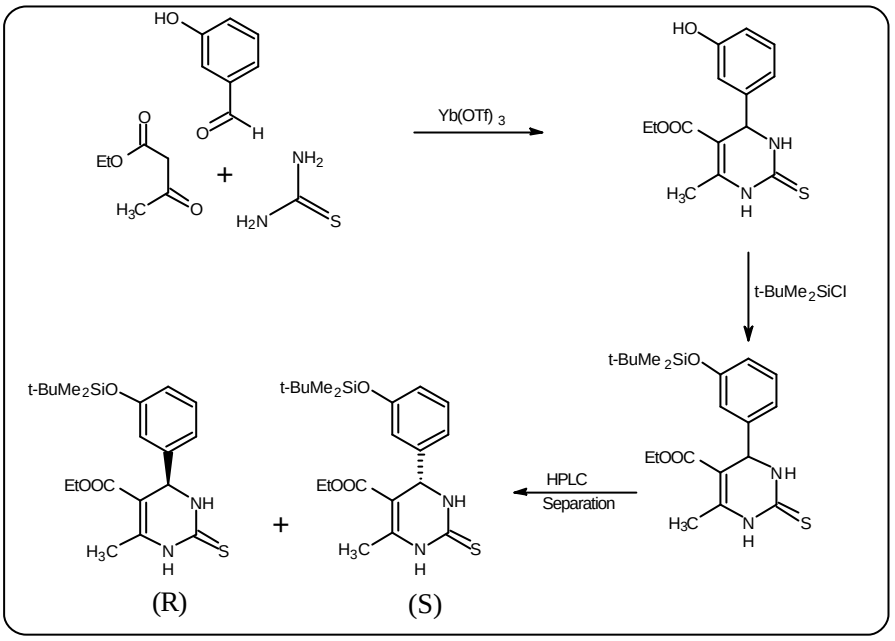


21

Out of a library of 16,320 diverse small molecules, Mayer et al.[70] identified monastrol as a lead compound for the development of new anticancer drugs. By using an innovative combination of two phenotype- based screens, one based on a mitosis-specific posttranslational modification and the other visualizing microtubules and chromatin, monastrol was recognized as the only cell-permeable compound that is capable of affecting mitosis in mammalian cells without targeting tubulin.

The design, synthesis and screening of libraries of small organic molecules possessing **privileged structures** has become a successful strategy in the drug discovery process.[72] The term **privileged structures** is generally used to describe those classes of small organic molecules (<600-700 molecular weight) that have been shown to possess the ability to bind to a wide range of receptors.[73] An efficient approach in medicinal chemistry relies on the identification of this type of scaffolds and their elaboration in a combinatorial manner with a set of pharmacophoric substituents to generate libraries of structurally related compounds. The biological screening of these collections then allows the identification of drug candidate compounds.[74] The

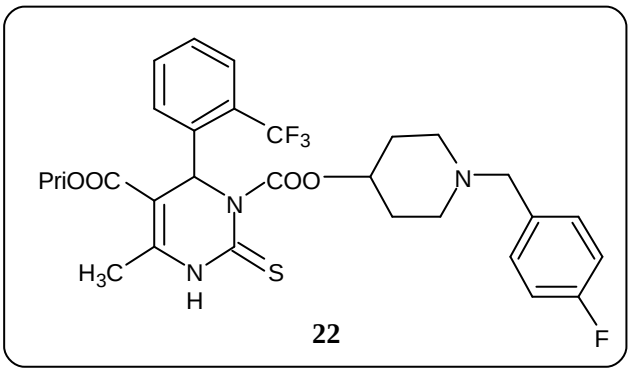
dihydropyrimidine (DHPM) ring represents a heterocyclic structure of remarkable biological efficiency, as well established through the pharmacological activities exhibited by various DHPM derivatives that have been identified as potent calcium channel modulators, orally active antihypertensive agents, antidiabetics andα_{1a}-adrenoreceptor-selective antagonists.[75]



Incidentally, DHPM derivatives are readily accessible products via the ketoester-aldehyde-urea (or thiourea) cyclocondensation known as the Biginelli three component reaction.[76] Quite recently, the DHPM derivative monastrol **(21)** was demonstrated to arrest mitosis in mammalian cells by causing the bipolar mitotic spindle to form a monoastral microtubule array surrounded by a ring of chromosomes.[70] This novel action of monastrol differentiates it from all other known mitotic inhibitors ranging from colchine to taxol, which instead affect microtubules, the main structural element of the mitotic spindle. Since its discovery in 1999, several papers have appeared in the literature reporting on the synthesis,[77,78] activity,[79-85] and enantiomeric separation[77,78,86] of monastrol and its analogues.[87] Focusing on factors important for bipolar spindle formation, it has been demonstrated that monastrol specifically inhibits *in vitro* and *in vivo* the motor

activity of the mitotic kinesin Eg5, a motor protein required for spindle bipolarity.[70,81] The rapid reversibility of monastrol inhibition activity allows for an exact temporal control over the cell cycle arrest in mitosis, thus confirming this small organic molecule as a new and powerful research probe of cellular processes.[88] Furthermore, since compounds that cause mitotic arrest have shown antitumor activity in humans,[88] monastrol may serve as a lead for the development of new anticancer drugs. A recent study established that, in the case of monastrol, the (S)-enantiomer is more active than both the (R)-enantiomer and the racemate.[81,82] Both (S)- and (R)-monastrols abolished basal Eg5ATPase activity, with the (S)-enantiomer demonstrating a 15-fold higher potency.[82]

George C. et al.[89] prepared dihydropyrimidine **(22)** was equipotent to nifedipine and amlodipine *in vitro*. In the spontaneously hypertensive rat, dihydropyrimidine **(22)** is both more potent and longer acting than nifedipine and compares most favorably with the long-acting dihydropyridine derivative amlodipine. Dihydropyrimidine **(22)** has the potential advantage of being a single enantiomer.

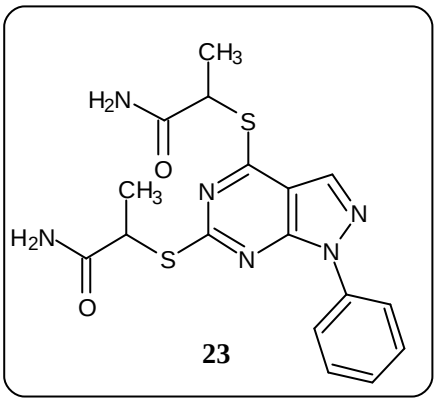


22

Edward J. et al.[90] employ difference infrared spectroscopy to probe structural changes that occur in the motor protein with monastrol in the presence of either ADP or ATP.

Sally Ann P. et al.[91] synthesized 4,6-Bis[(R-carbamoylethyl)thio]-1-phenylpyrazolo[3,4- d]pyrimidine **(23)** was identified as a novel adenosine A1receptor antagonist, antagonizing adenosine-stimulated cyclic adenosine monophosphate

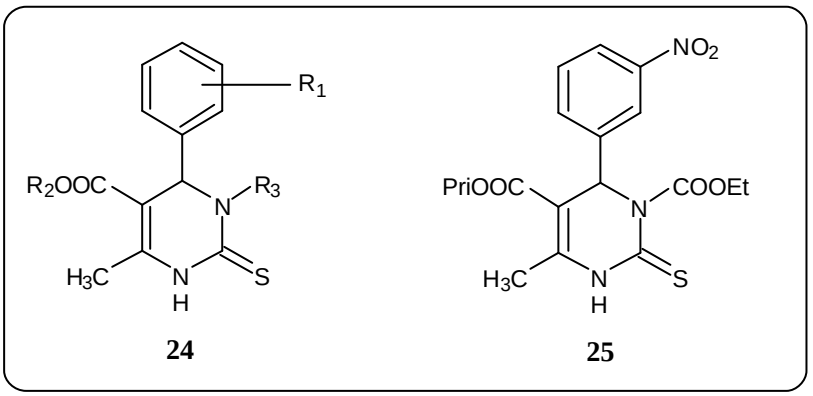
generation in guinea pig brain slices.[92,93]



23

Salvatore B. et al.[94] studied the stopped-flow fluorometry indicates that monastrol inhibits ADP release by forming an Eg5-ADP-monastrol ternary complex. Monastrol reversibly inhibits the motility of human Eg5. Monastrol has no inhibitory effect on the following members of the kinesin superfamily: MC5 (Drosophila melanogaster Ncd), HK379 (H. sapiens conventional kinesin), DKH392 (D. melanogaster conventional kinesin), BimC1-428 (Aspergillus nidulans BimC), Klp15 (Caenorhabditis elegans C-terminal motor), or Nkin460GST (Neurospora crassa conventional kinesin).

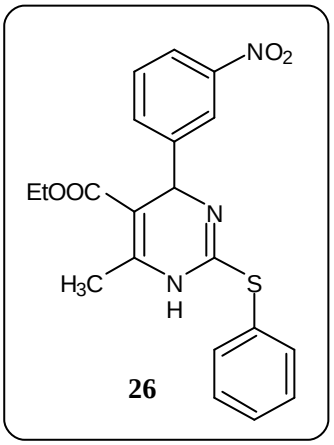
Atwal K. et al[62] synthesized the 3-substituted 1,4-dihydropyrimidine **(24)** and show that vasorelaxant activity was critically dependent on the size of the C5 ester group, isopropyl ester being the best, a variety of substituents (carbamate, acyl, sulfonyl, alkyl) were tolerated at N3. The dihydropyrimidines **(24)** are significantly more potent than corresponding 2-heteroalkyl-l,4-dihydropyrimidines. Dihydropyridine enantiomer usually show 10-15-fold difference in activity, the enantiomers of dihydropyrimidine **(25)**



24 **25**

show more than a 1000-fold difference in activity. These results strengthen the requirement of an enamino ester for binding to the dihydropyridine receptor and indicate a nonspecific role for the N3-substituent.

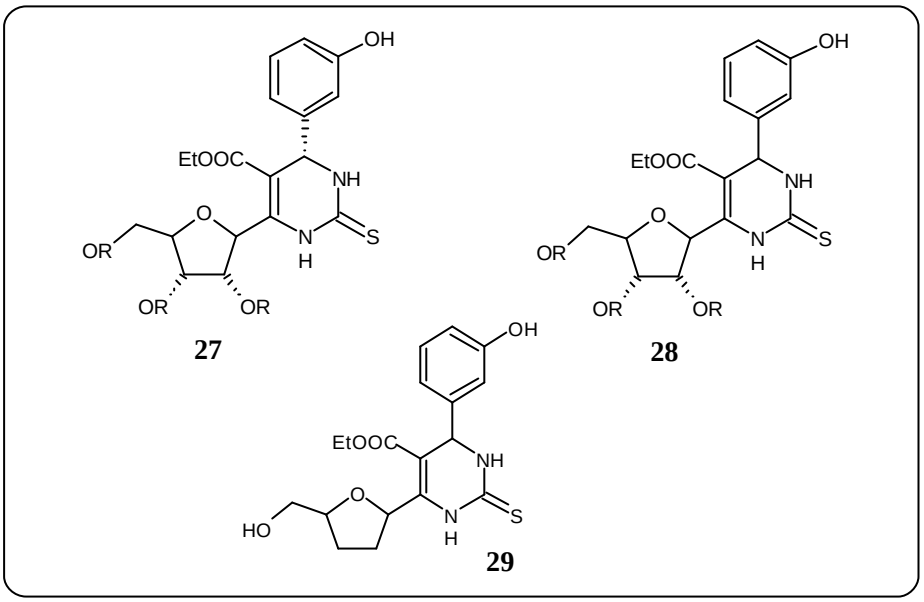
Atwal K.S.[56] prepared the 2-heterosubstituted-4-aryl-l,4-dihydro-6-methyl-5 pyrimidinecarboxylic acid esters which lack the potential C, symmetry of dihydropyridine calcium channel blockers, were prepared and evaluated for biological activity. Biological assays using potassium-depolarized rabbit aorta and radioligand binding techniques showed that some of these compounds are potent mimics of dihydropyridine calcium channel blockers. The combination of a branched ester (e.g. isopropyl, sec-butyl) and an alkylthio group (e.g. SMe) was found to be optimal for biological activity. Dihydropyrimidines **(26)** were found to be 30-fold less active. The solid-state structure of dihydropyrimidine analogue **(26)** shows that these compounds can adopt a molecular conformation which is similar to the reported conformation of dihydropyridine calcium channel blockers.



26

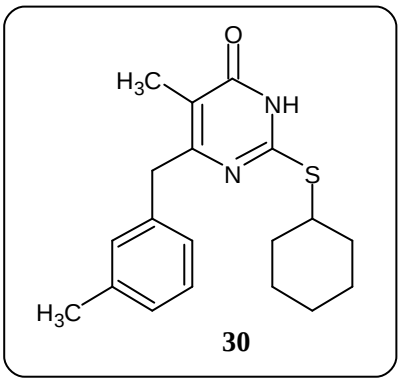
As a demonstration of this new concept in the Biginelli reaction, the synthesis of two C4 epimer monastrol analogues bearing the ribofuranosyl moiety at C6**(27),(28),(29)** has been synthesized by Alessandro D. et al.[95]

Novel compounds related to 2-(cyclohexylthio)-3,4-dihydro-5-methyl-6-(3-methylbenzyl)-4- oxopyrimidine **(30)** (MC 639) have been synthesized



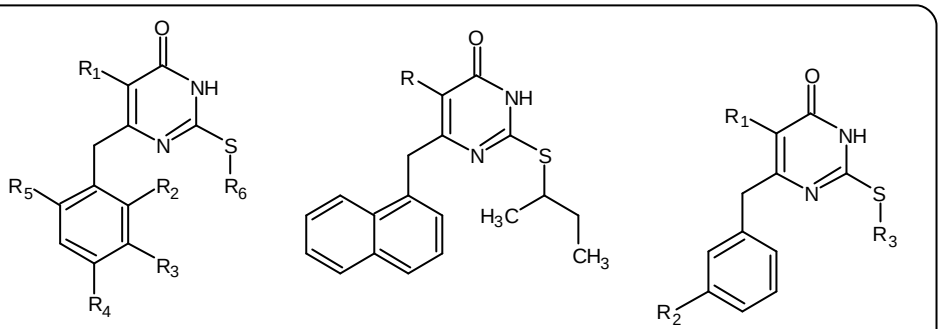
27 **28** **29**

by Antonello M. et al.[96] and tested as inhibitors of human immunodeficiency virus type-1 (HIV-1).



30

Numerous classes of nonnucleoside reverse transcriptase inhibitors (NNRTIs) have been discovered by Antonello Mai et al.[97] with dihydro-alkyloxy-benzyl-oxopyrimidines (DABOs) being one of them. The lead compound, an isotrimethoprim derivative **(31),(32),(33)** has been synthesized as a possible dihydrofolate reductase inhibitor, and when tested against HIV-1 because of its structural similarity with HEPT,[98,99] it was a selective, although not very potent, HIV-1 inhibitor.[100] On the basis of these findings, various oxopyrimidines have been synthesized and found to be specific HIV-1 inhibitors targeted at the reverse transcriptase.[101-104]



31

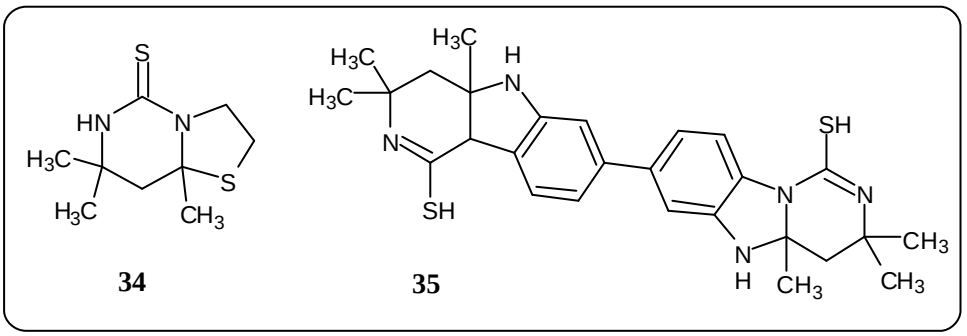
R 1 = H, Me
R 2-4 = Cl, F, NO2
R 5 = H, Cl, F
R 6 = alkyl, cycloalkyl

32 R = H, Me

33

R 1,2 = H, Me
R 3 = alkyl, cycloalkyl

Various 2-thiopyrimidine derivatives have been synthesized by Sondhi S.M. et al.[105] One of the compound, 7,7,8a-trimethyl-hexahydro-thiazolo[3,2-c]pyrimidine-5-thione **(34)** showed good anti-inflammatory (37.4% at 100mg/kg p.o.) and analgesic activity (75% at 100mg/kg p.o.). 7-(1-Mercapto-3,3,4a-trimethyl-4,4a,5,9b-tetrahydro-3H-pyrido[4,3-b]indol-7-yl)-3,3,4a-trimethyl-3,4,4a,5-tetrahydro-benzo[4,5]imidazo[1,2-c]pyrimidine-1-thiol **(35)** showed moderate activity against CDK-1 (IC(50)=5muM). The other compounds showed moderate anti-inflammatory (5-20%), analgesic (25-75%) and protein kinase (CDK-5, GSK-3) inhibitory activities (IC(50)>10muM).

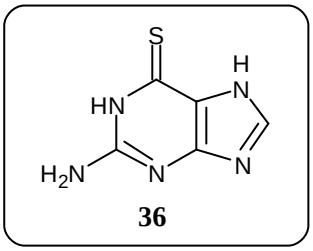


34 **35**

Massey A. et al.[106] described that 6-thioguanine (S6G) used in treatment of acute leukaemia. Its cytotoxic effect requires an active DNA mismatch repair (MMR) system. S6G is incorporated into DNA where a small fraction undergoes in situ conversion to

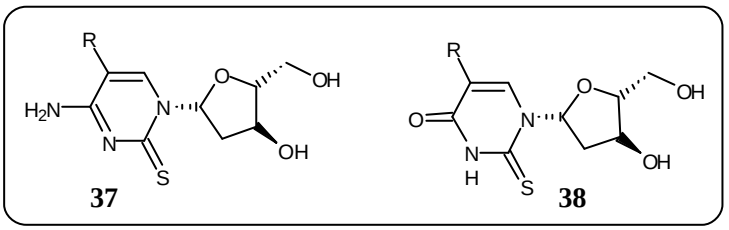
S6-thiomethylguanine (S6meG). After replication, S6meG-containing base pairs interact with MMR. This interaction is ultimately lethal and MMR-defective cells are resistant to S6G.

Massey A. et al.[106] report that growing human cells extensively incorporate the thiopyrimidine nucleoside 4-thiothymidine (S4TdR) into their DNA. The incorporated thiopyrimidine (S4T) can also undergo facile S-methylation to 4-thiomethylthymine (S4meT). The rate of methylation of S4TdR in model substrates is similar to that for the conversion of S6G to S6meG indicating that the DNA of cells grown in S4TdR will contain significant levels of S4meT.



36

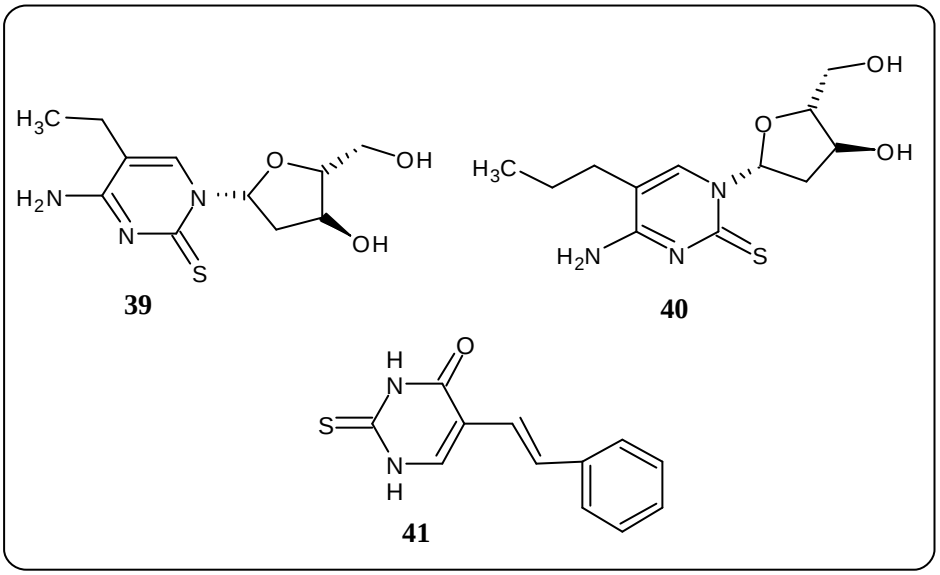
Twenty 5-alkyl-2-thiopyrimidine nucleosides were newly synthesized by Shigeta S. et al.[107] and examined for antiviral activities against herpes simplex virus (HSV), varicella-zoster virus VZV) and human cytomegalovirus (HCMV). In this study, 2'-deoxy-5-alkyl-2-thiocytidine **(37)** analogues had lower 50% effective concentration (EC50) values against HSV-1, and 2'-deoxy-5-alkyl-2-thiouridine **(38)** analogues showed lower



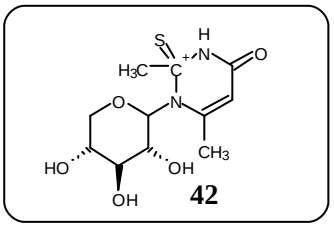
37 **38**

EC50 against VZV than their congeners of arabinoside form. Among the compounds examined, 2'-deoxy-5-ethyl and 5-propyl-2-thiocytidine **(39),(40)** were most potent and selective anti-HSV compounds. Their EC50s were 0.04 and 0.15

microM, and selectivity indexes were more than 7,215 and 1,849, respectively. On the other hand, 2'-deoxy-5-propyl-2-thiouridine , 5-bromovinyl-2-thiouracil arabinoside and 5-styryl-2-thiouracil arabinoside **(41)** were most potent and selective anti-VZV compounds. Their EC50s were 3.1, 3.8 and 2.6 pM for CaQu strain of VZV, respectively, and 2.1 to 3.0 times lower than that of acyclovir. All 2-thiopyrimidine nucleoside analogues did not show antiviral activities against thymidine kinase (TK) negative strains of HSV-1 and VZV. Only three 2-thiocytosine arabinoside compounds showed marginal anti-CMV activities (EC50s were 57-159 pM).

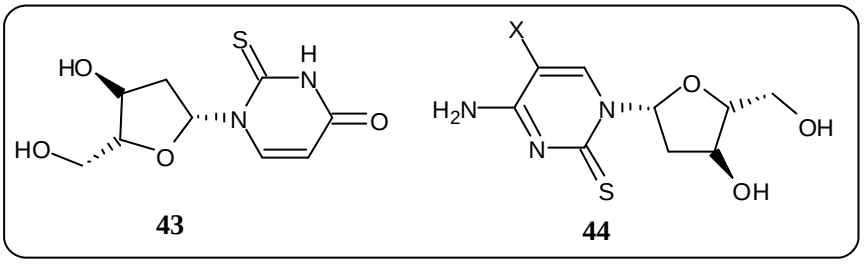


Attia A. M. et al.[108] synthesized N3-beta-D-glucopyranosyl, galactopyranosyl and xylopyranosyl 6-methyl-2-methylthiouracil **(42)** and their 5-bromo derivatives by coupling an α-acetobromosugar with the corresponding thiouracil. The new modified thiouridine analogues were evaluated for their inhibitory activity against Human Immunodeficiency Virus (HIV) replication in MT-4 cells as well as for their cytotoxicity.



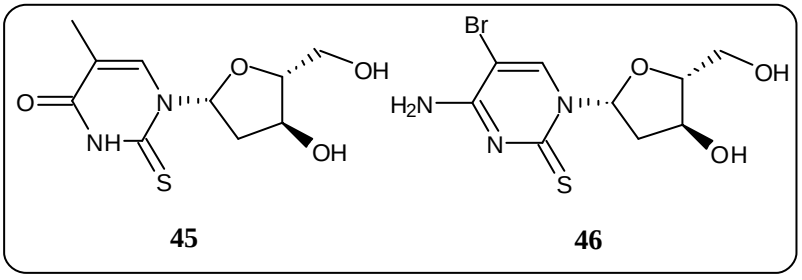
Twenty 2-thiopyrimidine nucleoside analogues were synthesized by Shigeta S. et al.[109] and examined for inhibitory activity against herpes simplex virus (HSV) type 1 and 2, varicella-zoster virus (VZV), human cytomegalovirus (HCMV) and thymidine kinase-deficient HSV (HSV-TK-) replication *in vitro*.

2-thiouracil (thymine) arabinoside, 2'-deoxy-2-thiouridine **(43)** and their 5-halogenated derivatives showed anti-HSV activity in both RPM18226 (human B-lymphoblastoid cells) and MRC-5 (human embryo lung cells). 2'-Deoxy-5-halogenated-2-thiocytidines **(44)** were also inhibitory against HSV, whereas 2-thiocytosine arabinoside and its derivatives were not inhibitory against HSV replication, except 5-bromo and 5-iodo congeners.



43 **44**

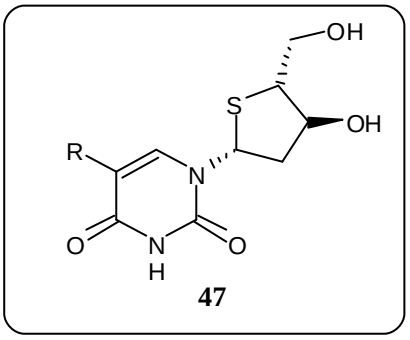
Substitution of the halogen atom at the 5-position of the pyrimidine rings to an atom with a higher molecular weight increased anti-HSV and VZV activities, except for the anti-HSV activity of 2-thiouracil arabinosides. 2'-Deoxy-5-methyl-2-thiouridines**(45)** showed the most potent anti-HSV activity, 2'-deoxy-5-chloro- and 2'-deoxy-5-bromo-2-thiocytidines **(46)** were potent inhibitors of VZV replication. However, none of the compounds inhibited HCMV and HSV-TK- replication. 5-Bromo and 5- iodocongenres were shown to inhibited HCMV and HSV-TK- as well as HSV and VZV



45 **46**

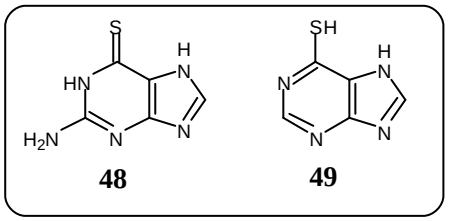
replication. The cytotoxicity of the 2-thio-pyrimidine nucleoside analogues was less than that of the 2-oxy-congeners of the compounds (5-iodo-2'-deoxyuridine, 5-iodo-2'-deoxycytidine, thymine arabinoside and cytosine arabinoside). The selectivity index of 2'-deoxy-5-iodo-2-thiouridine was higher than that of 5-iodo-deoxyuridine.The **compound of (45)** was not cytotoxic to resting or stimulated human peripheral blood mononuclear cells at 400 microM.

A series of 5-substituted 2'-deoxy-4'-thiopyrimidine nucleosides was synthesized by Rahim S. G. et al.[110] and evaluated as potential antiviral agents. A number of analogues such as 2'-deoxy-5-propyl-4'-thiouridine, 2'-deoxy-5-isopropyl-4'-thiouridine, 5-cyclopropyl-2'-deoxy-4'-thiouridine, 2'-deoxy-4'-thio-5-vinyluridine and 5-(2-chloroethyl)-2'-deoxy-4'-thiouridine **(47)** were found to be highly active against herpes simplex virus type-1 (HSV-1) and varicella zoster virus *in vitro* with no significant cytotoxicity. The compound with the broadest spectrum of activity was 2'-deoxy-5-ethyl-4'-thiouridine which showed significant activity against HSV-1, HSV-2 and VZV.



47

Massey A. et al.[111] described the thiopurines, 6-thioguanine **(48)** and 6-mercaptopurine, **(49)** are antileukemic agents that are incorporated into DNA following retrieval by the purine salvage pathway.

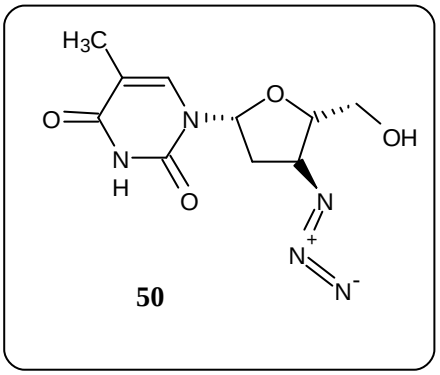


48 **49**

Their toxicity requires active DNA mismatch repair (MMR) and thiopurine resistance is an acknowledged phenotype of MMR-defective cells. In addition to these direct cytotoxic effects, DNA thiobases have distinctive photochemical properties , the therapeutic potential of which has not been extensively evaluated.

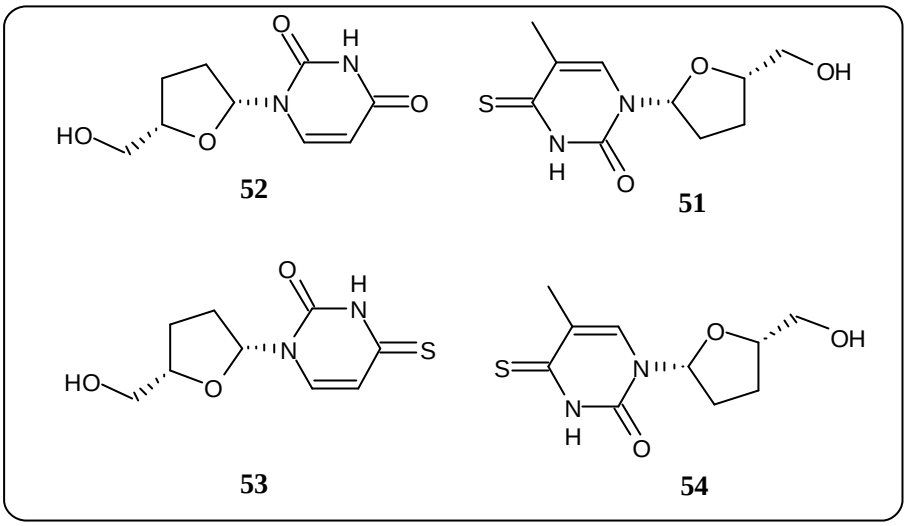
Novel D- and L-2'-azido-2',3'-dideoxy-4'-thionucleosides were synthesized by Jeong L.S. et al.[112] and evaluated for antiviral activity. When the final nucleosides were tested against HIV-1, HSV-1, HSV-2 and HCMV they were found to be only active against HCMV without cytotoxicity up to 100 micrograms/ml.

Oxygen-sulfur exchange at the C-4 carbonyl of several modified pyrimidine nucleosides, including 3'-azido-3'-deoxythymidine (AZT)**(50)**, is described in an effort to enhance the lipophilicity and thereby, the delivery to the central nervous system of the sulfur analogues without compromising the anti-HIV activities of the parental structures.



50

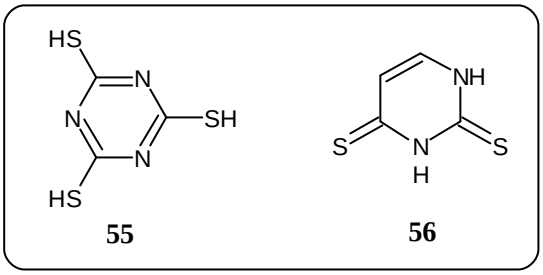
Compounds 2',3'-didehydro-3'-deoxy-4-thiothymidine **(51),** 2',3'-didehydro-2',3'-dideoxyuridine **(52)**, 2',3'-dideoxy-4-thiouridine **(53)** and 3'-deoxy-4-thiothymidine **(54)** were evaluated for their effects on HIV-induced cytopathogenicity of MT-2 and CEM cells by Palomino E. et al.[113] Only **(51)** and **(54)** were moderately active in protecting both cell lines against the cytolytic effect of HIV. The inhibitory effects of analogues **(51)**, **(52)**, **(53)** and **(54)** on thymidine phosphorylation by rabbit thymus thymidine kinase were evaluated. Only**(53)** showed moderate affinity (Ki = 54 microM) for the enzyme.



Yamamoto Y. et al.[114] shows that the steric effects of the 2-thiocarbonyl group and the 2'-hydroxyl group cause the rigidity of the C3'-endo-gg form of 2-thioribothymidine(s2T) . Such rigidity of s2T probably contributes to the thermostability of 2-thiopyrimidine polyribonucleotides and extreme thermophile tRNAs.

A new thiopyrimidine derivative has been synthesized by Bassleer R. et al.[115] It can inhibit cell multiplication in Chick embryo fibroblasts, in Mouse Ehrlich ascites tumor cells and in Rat hepatoma cells (line Rueber) cultivated *in vitro*.

One hundred compounds were evaluatedby Max H. et al.[116] as ligands of *Toxoplasma gondii* uracil phosphoribosyltransferase (UPRTase, EC 2.4.2.9) by examining their ability to inhibit this enzyme *in vitro*. Inhibition was quantified by determining apparent K_i values for those compounds that inhibited *T. gondii* UPRTase by greater than 10% at a concentration of 2 mM. Five compounds (4-thiopyridine, 2-thiopyrimidine, trithiocyanuric acid **(55)**, 1-deazauracil and 2,4-dithiouracil **(56)**) bound to the enzyme better than two known substrates for *T. gondii* UPRTase, 5-fluorouracil and emimycin, which have antitooplasmal activity.[117,118] In addition, several selected compounds were evaluated as substrates for *T. gondii* UPRTase, and it was found that 2,4-dithiouracil is also a substrate for this enzyme.

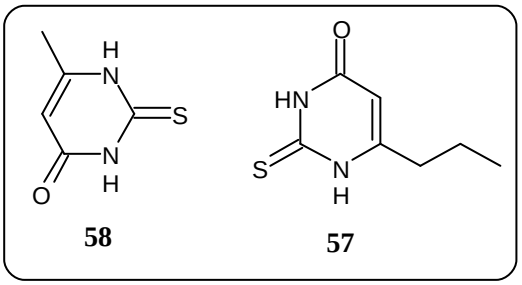


55 **56**

Transfer RNAs isolated by Kwong L. K. et al.[119] from Escherichia coli B grown in the presence of 2-thiouracil are deficient in pseudouridine. Much of this deficiency is from the T psi C region, which has only about 50% of its normal pseudouridine content. The other modified nucleoside from this region, ribothymidine, is reduced by only about 10%. Studies showed that 2-thiouracil is incoproated into the RNA of E. coli during growth in the presence of the analog.

New thiopyrimidine derivatives have been synthesized by Bassleer R. et al.[120] Among them, several inhibit the multiplication of Chick embryo cells cultivated*in vitro* they provoke strong nucleolar alterations, prevent the cells from entering into mitosis and can give rise to cell polyploidisation as to DNA.

Raymond H. et al.[121] described that mouse kidney thiol transmethylase and *S*-adenosylmethionine were incubated with the radioactive antithyroid drugs, 2-thiouracil (TU), 6-propyl-2-thiouracil **(57)** (PTU), methimazole (MMI). 6-Methyl-2-thiouracil **(58)** (6-methyl TU) or thiourea. Radioactive metabolites were produced with TU, PTU and 6-methyl TU and, in each case. were identified as the corresponding*S*-methyl derivatives. No measurable metabolism of MMI or thiourea was observed.

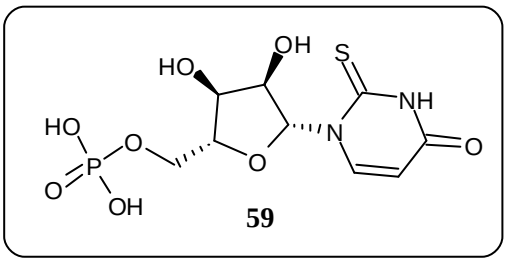


58 **57**

The results obtained demonstrate that *S*-methylation is a general pathway of metabolism for thiopyrimidine antithyroid drugs, but not for thiourea or MMI, which markedly decreases the antiperoxidase activity of the parent compound.

HeLa cells infected with radioactive poliovirus type 2 were disrupted with ultrasonic treatment, followed by addition of a non-ionic detergent. Two types of virus particles were found to sediment at 80 to 90% the rate of native virus. The first of these appeared to be a complex of native virus particles and membrane components, since treatment with 0-2% SDS released infectious native particles. The second was non-infectious and its sedimentation rate was not greatly altered by SDS. One hour after infection this non-infectious particle was the major product of cell-mediated eclipse. Lonberg-Holm K. et al.[122] have confirmed that 10 to 30 mg-g/ml S-7, a substituted thiopyrimidine, blocks infection of cells by poliovirus in a specific manner.

Mazumdar K. et al.[123] analyzed the X-ray fibre diffraction pattern obtained from synthetic poly-2-thiouridylic acid (poly(s2U)) **(59)**, a 2-thiosubstituted homologue of polyuridylic acid, reveals that the poly(s2U) homopolymer exists in a structure similar to that of *A*-DNA

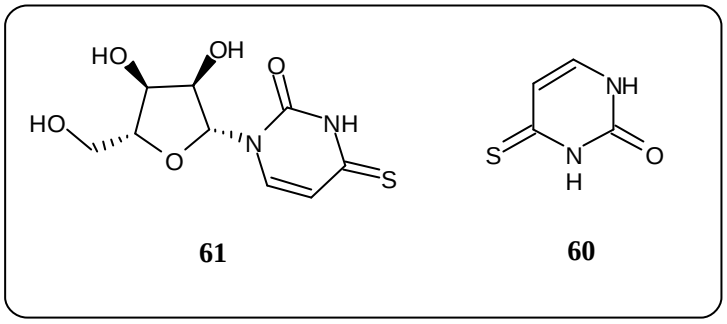


59

Further, yeast $tRNA_3Glu$ contains a 2-thiouridine derivative in the 32 -position of its anticodon and recognizes GAA but not GAG as the codon for glutamic acid. This specificity can be explained when considering the preferred S · · · N stacking interactions which would restrict “wobbling” of the 32 -nucleotide of the anticodon.

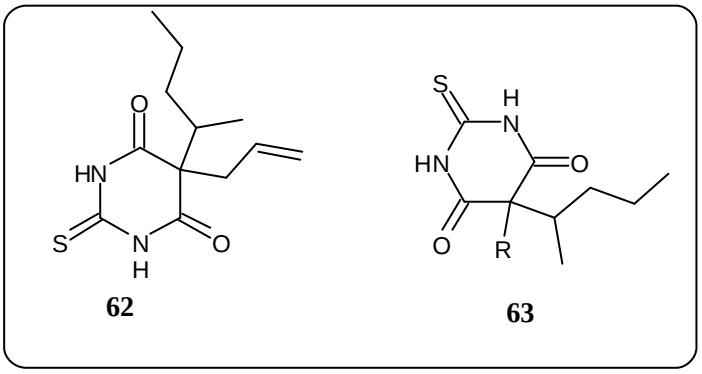
Bo Sorbo et al.[124] described that 4-Thiouracil **(60)**, 4-thiouridine **(61)** and tRNA from *Escherichia coli* were irradiated with X-rays in air-saturated solutions and the

radiolysis of the 4-thiouracil moieties was determined spectrophotometrically. The dose-effect curves were exponential, giving initial yields of destruction (*G* value) of 3.22 for thiouracil, 2.45 for thiouridine and 0.31 for the thiouracil residues in tRNA. The thiopyrimidine residues were more radiolabile than the corresponding oxygen analogues, as the *G* values found for uracil and uridine under the same conditions were 2.28 and 1.83, respectively.



61 **60**

The metabolic fate of three pharmacologically significant thiopyrimidines has been investigated by Spector E. et al.[125] Incubation of thiamylal **(62)**, 5-allyl-5-(1-methylbutyl)-2-thiobarbituric acid **(63)**, with minced rat liver resulted in the formation of a metabolite which was isolated and identified as secobarbital.



62 **63**

The urine of rats receiving thiouracil, 2-mercapto-4hydroxypyrimidine was examined by ion exchange and paper chromatography and revealed significant amounts of uracil. Thiouracil, when incubated with a mince or homogenate of rat liver, was metabolized at the rate of 280–350 *g*/*g* of tissue per 3 hr.

With an intention of preparing the compounds possessing better therapeutic activity, we have undertaken the synthesis of dihydropyrimidinthiones which have been described in following sections

SECTION-I **SYNTHESIS AND BIOLOGICAL SCREENING OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDRO PYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES.**

SECTION-II **SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDRO PYRIMIDIN-2(1H)-THIONE-5-CARBOXYLATES.**

SECTION-III **SYNTHESIS AND BIOLOGICAL SCREENING OF N-(2,4-DI CHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES.**

SECTION-IV **SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES.**

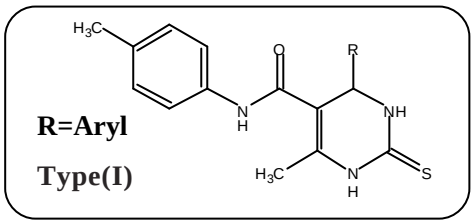
SECTION-V **SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXAMIDES.**

SECTION-VI **SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXY PHE NYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES.**

SECTION - I

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES.

Much interest have been focused around dihydropyrimidinone derivatives because of their wide variety of pharmacologidal properties and industrial applications. In view of these findings and achieve to bettr drug potency, we have synthesized 6-Methyl-N-(4-methylphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxamides of Type (I) by the cyclocondensation of N-(4-methylphenyl)-3-oxobutanamide with thiourea and aryl aldehydes.



R=Aryl

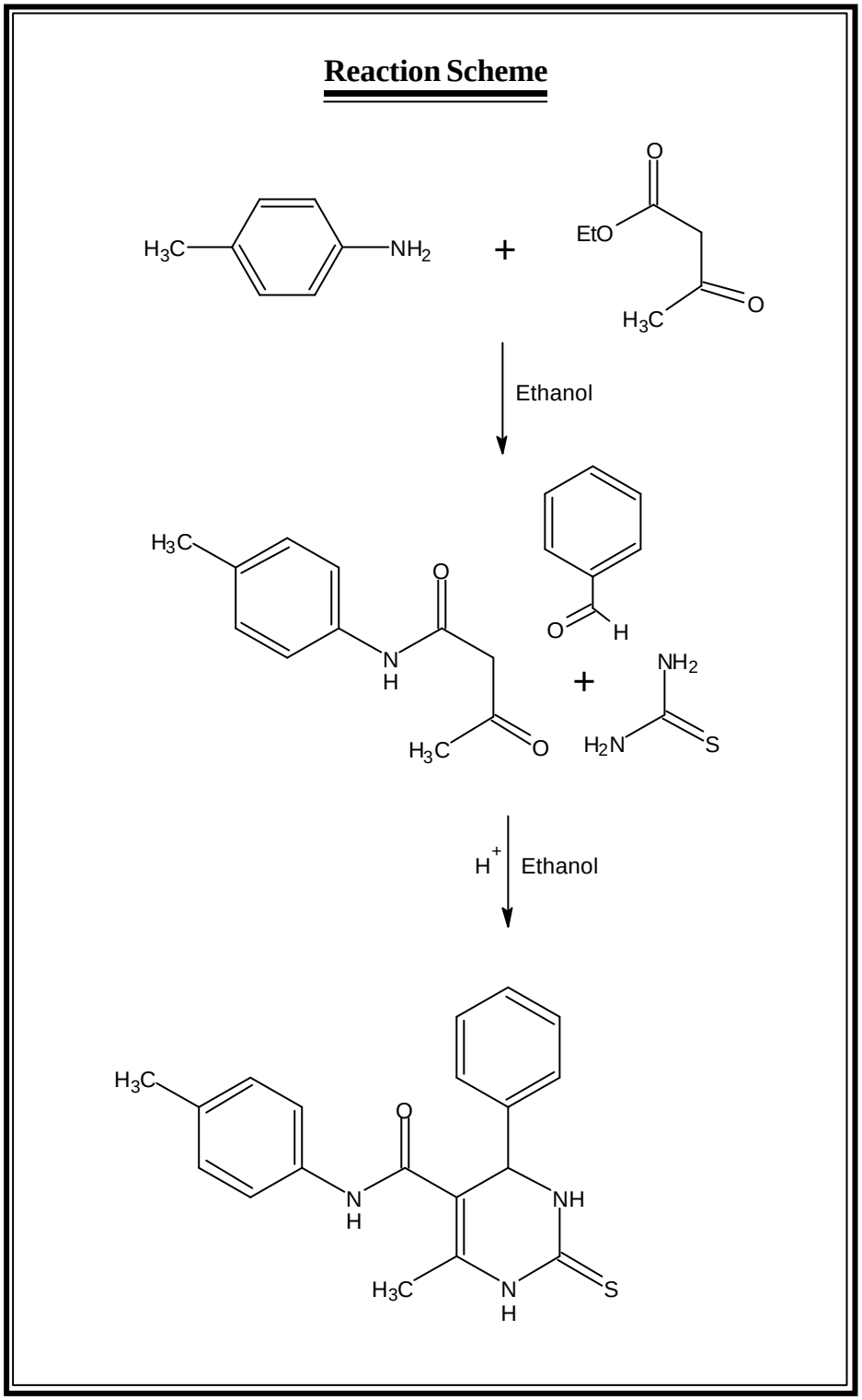
Type(I)

The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

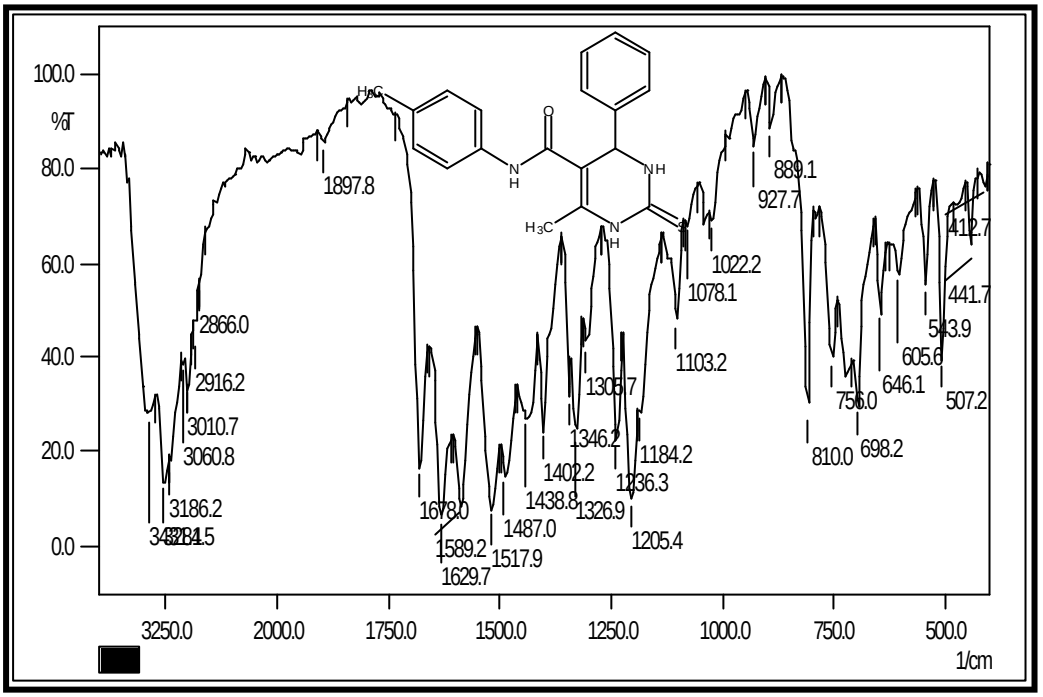
All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Moreover, some selected compounds have been evaluated for their ***in vitro*** biological assay towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at a concentration of 6.25 µg/ml using Rifampin as a standard drug which have been tested at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF), Alabama, U. S. A.

Reaction Scheme



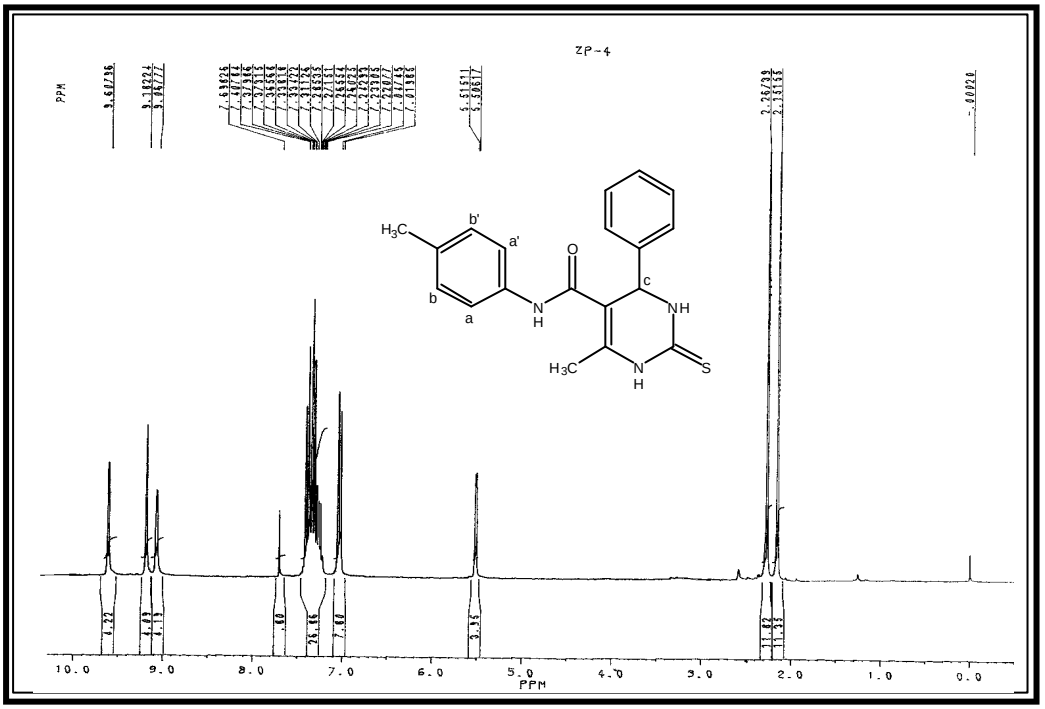
NMR SPECTRAL STUDIES OF 6-METHYL-N-(4-METHYLPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDE.



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2916	2975-2950	126
$-CH_3$	C-H str. (sym.)	2866	2880-2860	,,
	C-H i.p.def. (asym.)	1438	1470-1435	,,
	C-H o.o.p. def. (sym.)	1326	1390-1370	,,
Aromatic	C-H str.	3010	3090-3030	127
	C=C str.	1487	1540-1480	,,
		1402	1520-1480	,,
	C-H i.p. (def.)	1078	1125-1090	,,
	C-H o.o.p. (def)	810	835-810	,,
Pyrimidine	C=C str.	1589	1580-1520	,,
moity	C-H str.	3060	3080-3030	,,
	C-H i.p. def.	1103	1125-1090	,,
Amine	-NH str.	3431	3410-3380	126
	-NH def.	1629	1635-1595	,,
Amide	- C=O str	1678	1690-1660	,,

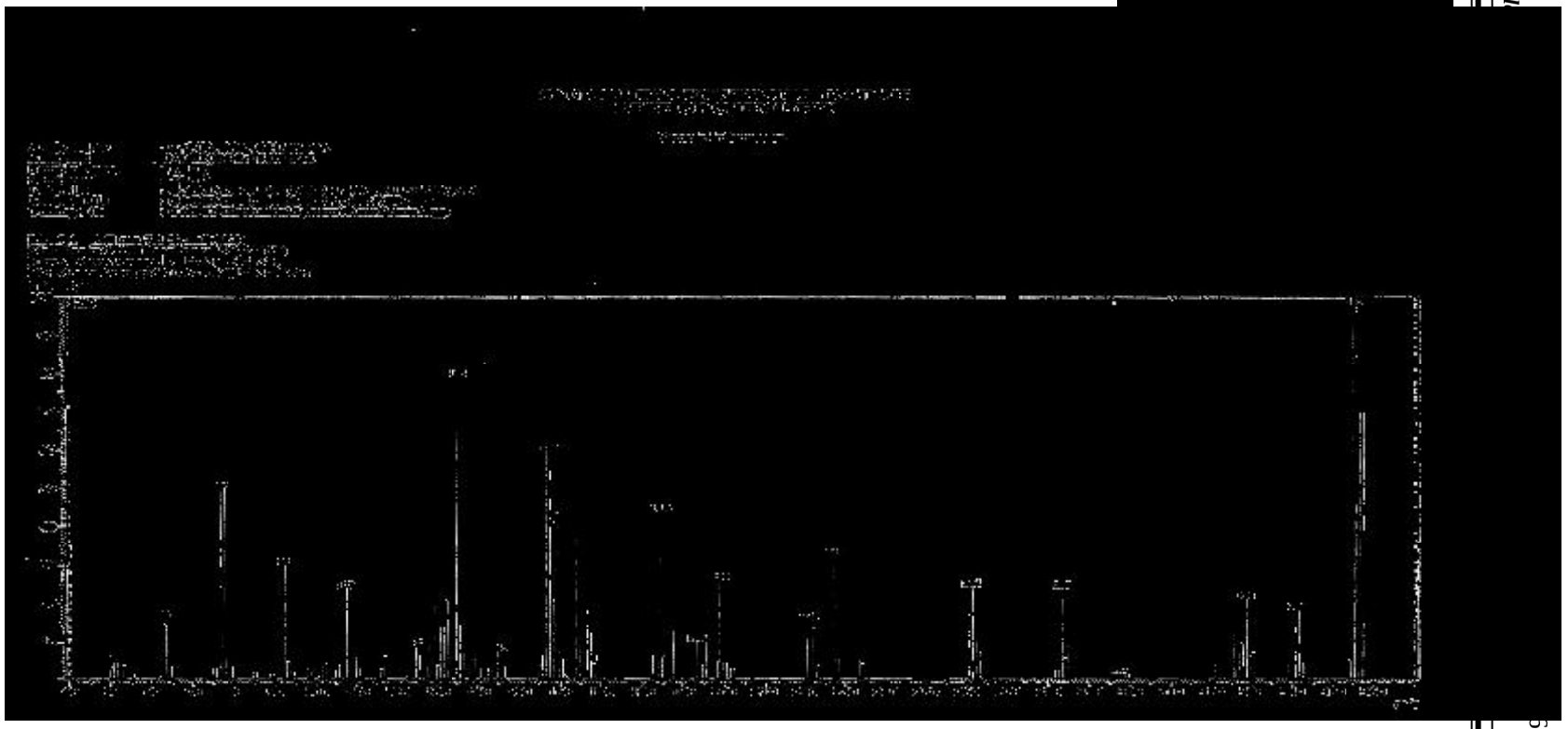
NMR SPECTRAL STUDIES OF 6-METHYL-N-(4-METHYLPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.15	3H	singlet	$-CH_3$(Pyr.)	-
2	2.26	3H	singlet	Ar-CH_3	-
3	5.50	1H	singlet	Ar-Hc	-
4	7.01-7.04	2H	doublet	Ar-Ha,a'	Jaa'=9.0
5	7.31	5H	multiplate	Ar-H	-
6	7.37-7.40	2H	doublet	Ar-Hb,b'	Jbb'=9.0
7	9.06	1H	singlet	-NH(Amide)	-
8	9.18	1H	singlet	-NH(Pyr.)	-
9	9.60	1H	singlet	-NH(Pyr.)	-

MASS SPECTRAL STUDIES OF 6-METHYL-N-(4-METHYLPHENYL)-4-(4-FLUOROPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES.

(A) Synthesis of N-(4-methylphenyl)-3-oxobutanamide.

See Part-I, Section-I (A).

(B) Synthesis of 6-Methyl-N-(4-methylphenyl)-4-phenyl-3,4-dihydro pyrimidin-2(1H)-thione-5-carboxamide.

A mixture of thiourea (0.76 gm, 0.01 mol), benzaldehyde (1.06 gm, 0.01 mol) and N-(4-methylphenyl)-3-oxobutanmide (1.91 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^0C. The resulting solid mass separated was filtered and crystallized from dioxane. Yield 41%, m. p. 242^0C, Anal.Calcd. for $C_{19}H_{19}N_3OS$ Calcd: C, 67.63; H, 5.68; N, 12.45%, Found: C, 67.61; H, 5.67; N, 12.44%.

Similarly, other 6-Methyl-N-(4-methylphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxamides were prepared. The physical data are recorded in Table No. 7

(C) Biological screening of 6-Methyl-N-(4-methylphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxamides.

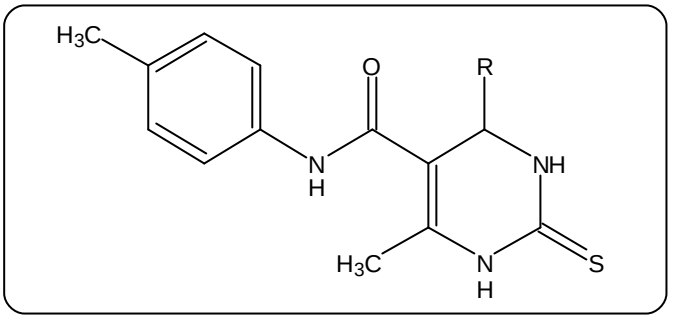
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.7

TABLE-7 : PHYSICAL CONSTANTS OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
7a	C_6H_5-	$C_{19}H_{19}N_3OS$	337	242	41	12.45	12.44	0.51	S1
7c	2-Cl-C_6H_4-	$C_{19}H_{18}ClN_3OS$	371	278	35	11.30	11.28	0.53	S1
7c	3-Cl-C_6H_4-	$C_{19}H_{18}ClN_3OS$	371	236	38	11.30	11.27	0.56	S2
7d	4-F-C_6H_4-	$C_{19}H_{18}FN_3OS$	355	302	37	11.82	11.78	0.45	S1
7e	2-NO_2-C_6H_4-	$C_{19}H_{18}N_4O_3S$	382	245	41	14.65	14.61	0.54	S2
7f	3-NO_2-C_6H_4-	$C_{19}H_{18}N_4O_3S$	382	321	47	14.65	14.62	0.51	S2
7g	3-OCH_3 -C_6H_4-	$C_{20}H_{21}N_3O_2S$	367	258	45	11.44	11.42	0.42	S1
7h	4-OCH_3 -C_6H_4-	$C_{20}H_{21}N_3O_2S$	367	214	47	11.44	11.41	0.55	S2
7i	2-OH-C_6H_4-	$C_{19}H_{19}N_3O_2S$	353	258	42	11.89	11.86	0.42	S1
7j	4-OH -C_6H_4-	$C_{19}H_{19}N_3O_2S$	353	246	40	11.89	11.84	0.48	S2
7k	2,5-$(OCH_3)_2$-C_6H_3-	$C_{21}H_{23}N_3O_3S$	397	287	37	10.57	10.55	0.54	S2
7l	3-C_6H_5-O-C_6H_4-	$C_{25}H_{23}N_3O_2S$	429	301	48	9.78	9.75	0.46	S1

S1 Hexane:Ethyl acetate(8:2), S2 Hexane:Ethyl acetate(5:5)

ANTITUBERCULAR ACTIVITY OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES.



TAACF, Southern Research Insitute

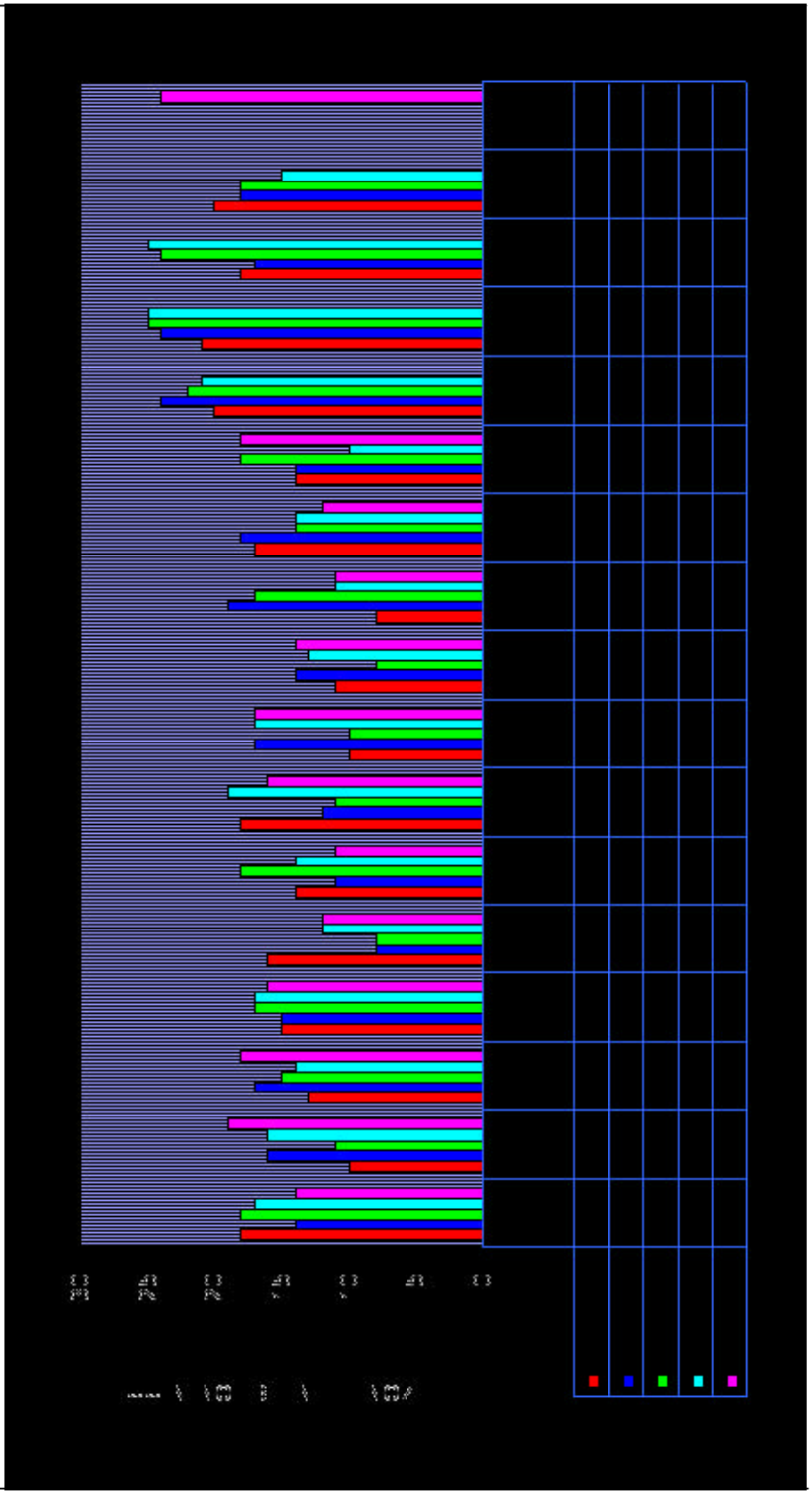
TABLE NO-7

Primary Assay Summary Report

Sr. No.	Sample ID	Corp ID	R	Assay	Mtb Strain	MIC mg/ml	% Inhibi.
7a	179650	ZP-14	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	00
7b	179651	ZP-15	2-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	25
7c	179652	ZP-16	3-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	09
7d	179653	ZP-17	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	19
7e	179654	ZP-18	2-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	33
7f	179655	ZP-19	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
7g	179656	ZP-20	$C_{10}H_7$-	Alamar	$H_{37}Rv$	>6.25	61
7h	179657	ZP-21	3-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
7i	179658	ZP-22	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	07
7j	179659	ZP-23	2,5-$(OCH_3)_2$-C_6H_3-	Alamar	$H_{37}Rv$	>6.25	00
7k	179660	ZP-24	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	30
7l	179661	ZP-25	3-C_6H_5O-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	27

NAID/Southern Research Insitute/GWL Hansen's Disease Centre/Colorado State University proprietary Information

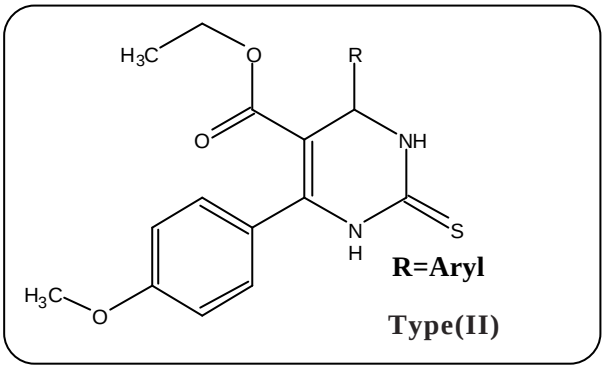
GRAPHICAL CHART NO. 7 : ANTIMICROBIAL ACTIVITYS OF 6-METHYL-N-(4-METHYLPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES



SECTION - II

SYNTHSIS AND BIOLOGICAL SCREENING OF ETHYL-6-(4-METHOXY PHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXYLATES.

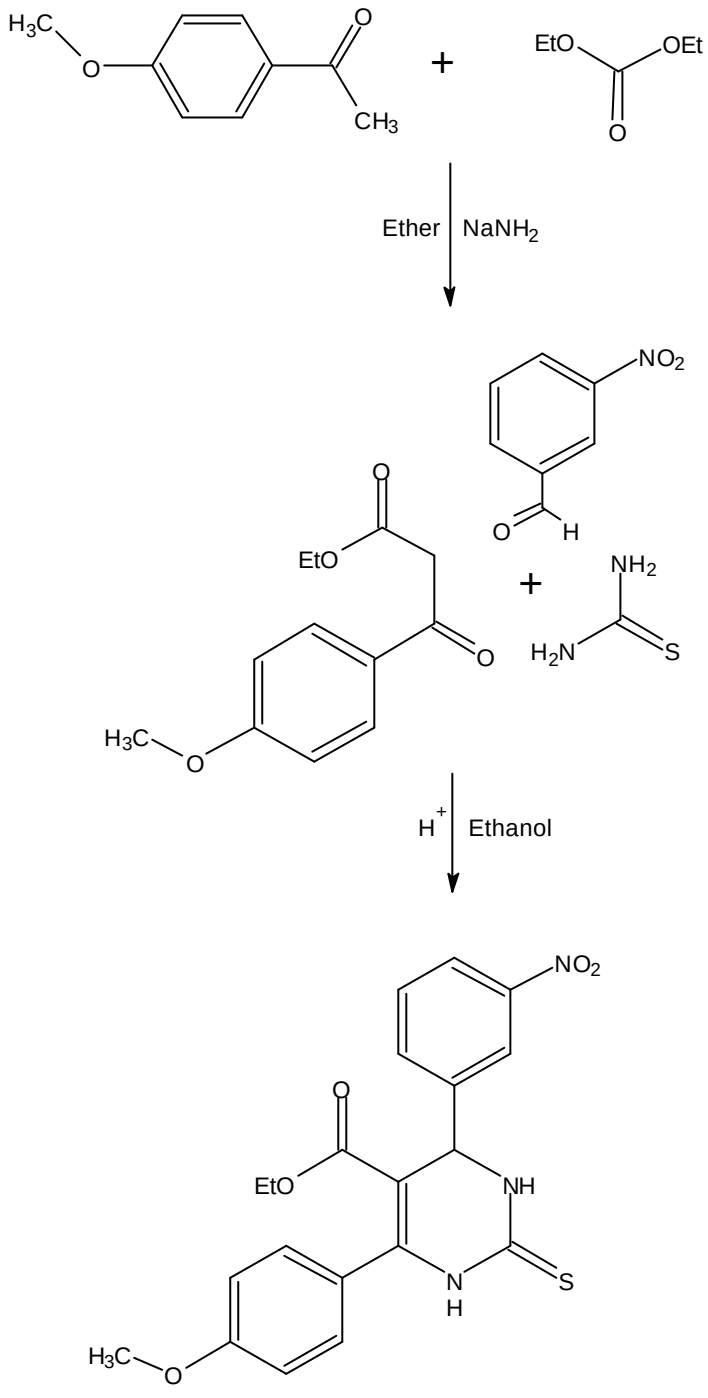
Compounds containing pyrimidine ring are widely distributed in nature. Many of these derivatives are reported to possess different biological activities. In view of these report, we have synthesized Ethyl-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxylates of Type (II) by the condensation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate, thiourea and aryl aldehydes.



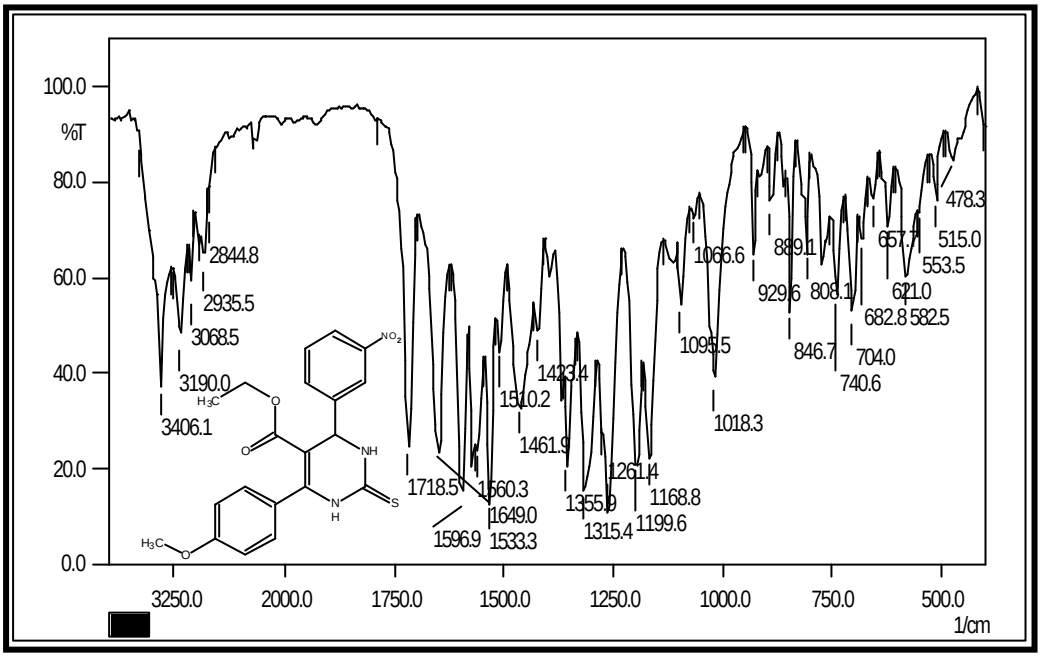
The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Reaction Scheme



IR SPECTRAL STUDIES OF ETHYL-6-(4-METHOXYPHENYL)-4-(3-NITROPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXYLATE.

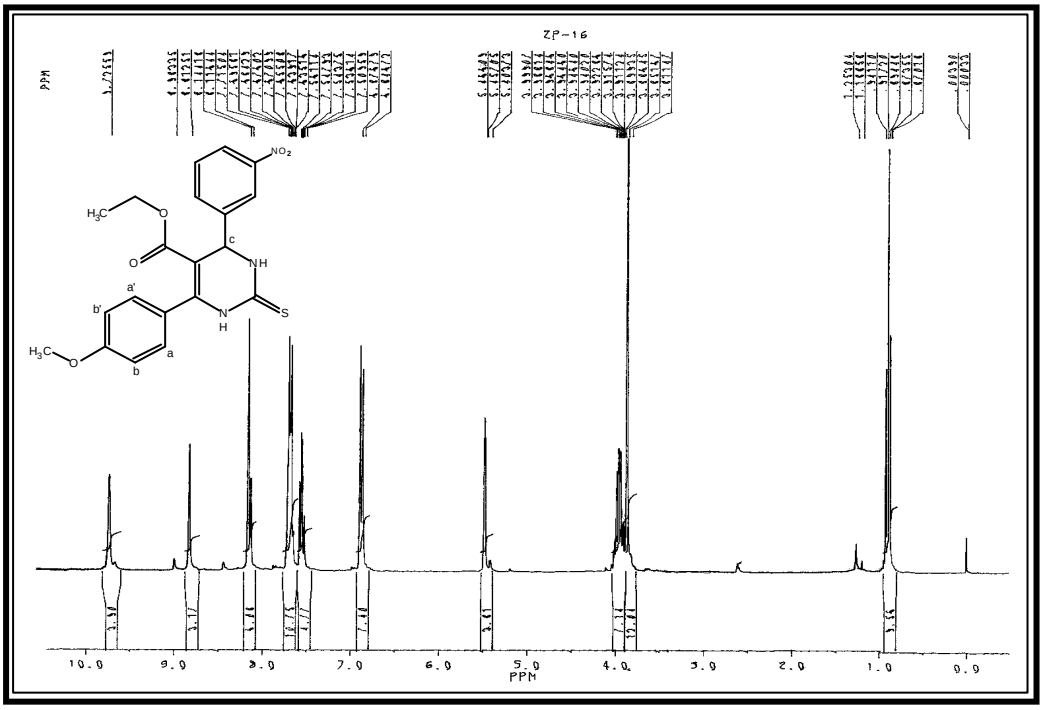


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}

(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2935	2975-2950	126
$-CH_3$	C-H str. (sym.)	2844	2880-2860	,,
	C-H i.p.def. (asym.)	1423	1470-1435	,,
	C-H o.o.p. def. (sym.)	1355	1390-1370	,,
Aromatic	C-H str.	3190	3090-3030	127
	C=C str.	1510	1540-1480	,,
		1461	1520-1480	,,
	C-H i.p. (def.)	1095	1125-1090	,,
	C-H o.o.p. (def)	808	835-810	,,
Pyrimidine	C=C str.	1596	1580-1520	,,
moity	C-H str.	3068	3080-3030	,,
	C-H i.p. def.	1066	1125-1090	,,
Amine	-NH str.	3406	3410-3380	126
	-NH def.	1649	1635-1595	,,
Ester	- C=O str	1718	1690-1660	,,

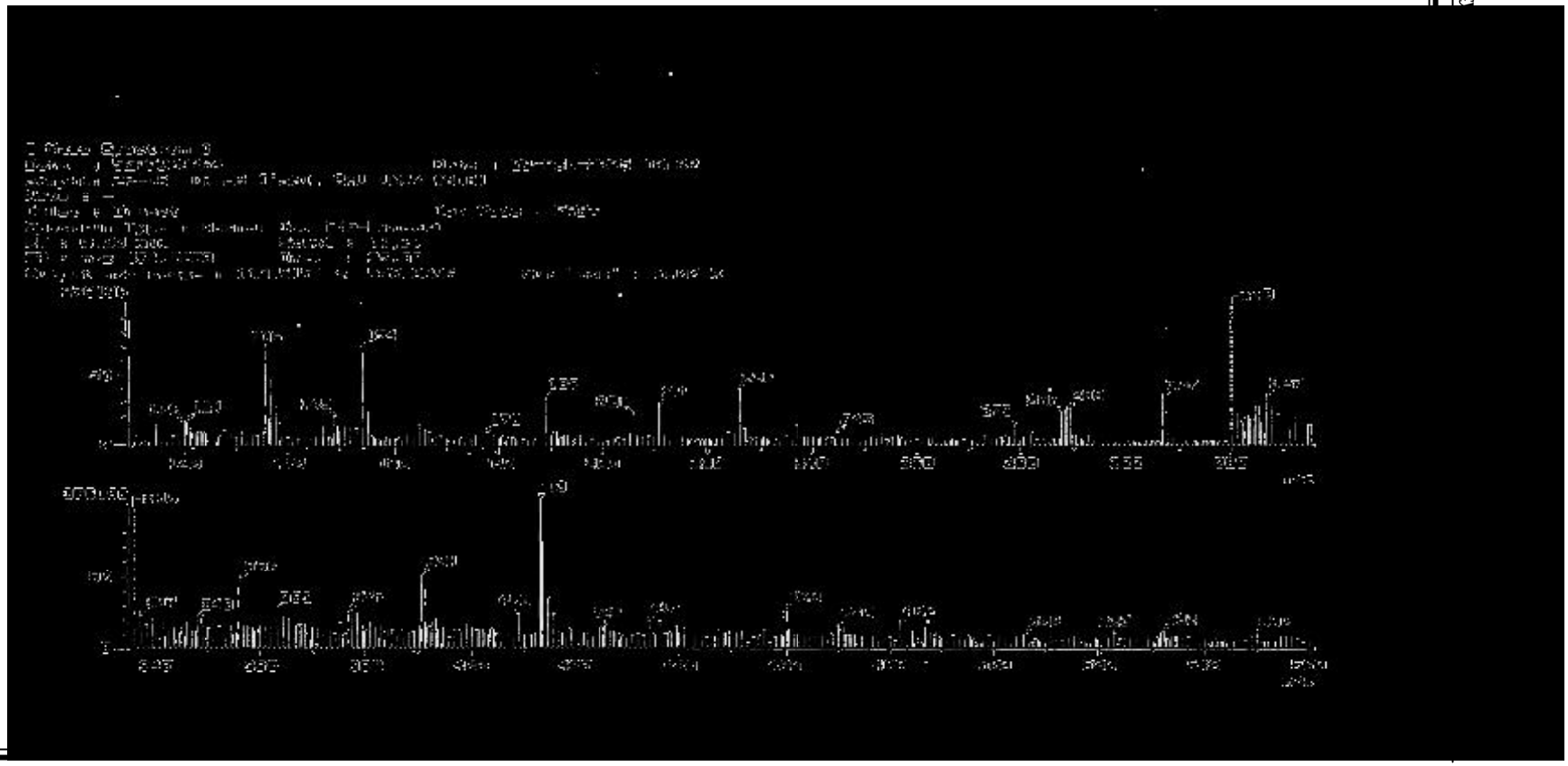
NMR SPECTRAL STUDIES OF ETHYL-6-(4-METHOXYPHENYL)-4-(3-NITROPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXYLATE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	0.91	3H	triplet	$-CH_3$	-
2	3.61	3H	singlet	$Ar-OCH_3$	-
3	3.91	2H	quatret	$-CH_2$	-
4	5.46	1H	singlet	Ar-Hc	-
5	6.84-6.87	2H	doublet	Ar-Hb,b'	Jaa'=9.0
6	7.50-7.71	5H	multiplet	Ar-H	
7	8.71-8.74	2H	doublet	Ar-Ha,a'	Jbb'=9.0
8	8.96	1H	singlet	NH(Pyr.)	-
9	9.72	1H	singlet	NH(Pyr.)	-

MASS SPECTRAL STUDIES OF ETHYL-6-(4-METHOXYPHENYL)-4-(3-NITROPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXYLATE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-6-(4-METHOXY PHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXYLATES.

(A) Synthesis of Ethyl-3-(4-methoxyphenyl)-3-oxopropanoate.

See Part-I, Section-II (A).

(B) Synthesis of Ethyl-6-(4-methoxyphenyl)-4-(3-nitrophenyl)-3,4-dihydro pyrimidin-2(1H)-thione-carboxylate.

A mixture of thiourea (0.76 gm, 0.01 mol), m-nitrobenzaldehyde (1.51 gm, 0.01 mol) and ethyl-3-(4-methoxyphenyl)-3-oxopropanoate (2.22 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^0C. The resulting solid mass separated was filtered and, crystallized from dioxane.Yield 47%, m.p.247^0C, Anal.Calcd. for $C_{20}H_{19}N_3O_5S$ Calcd: C,58.10; H, 4.63; N, 10.16%, Found: C, 58.9; H, 4.62; N, 10.14%.

Similarly, other Ethyl-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxylates were prepared. The physical data are recorded in Table No. 8

(C) Biological screening Ethyl-6-(4-methoxyphenyl)-4-aryl-3,4-dihydro-pyrimidin-2(1H)-thione-5-carboxylates.

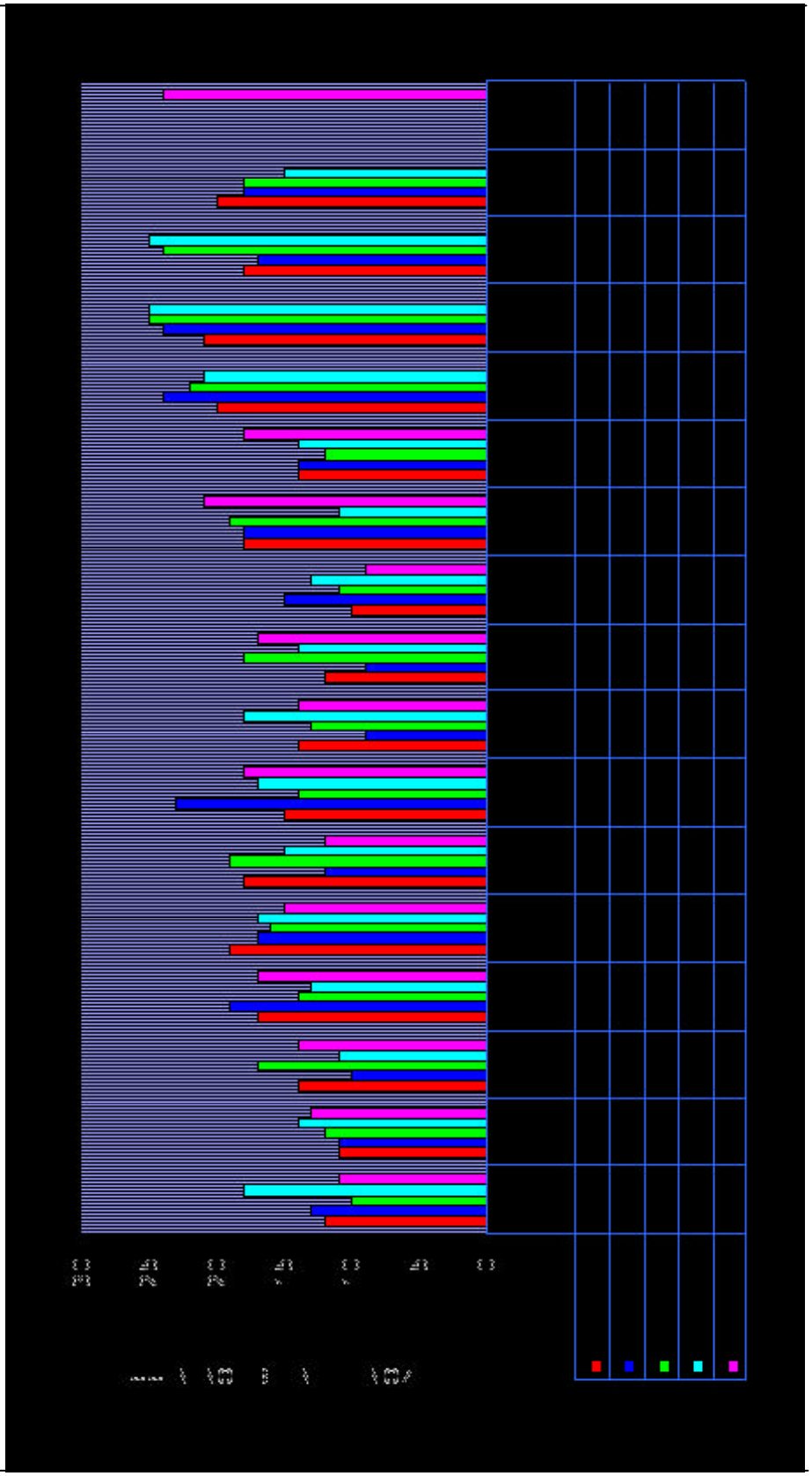
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.8

TABLE-8 : PHYSICAL CONSTANTS OF ETHYL-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXYLATES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
8a	C_6H_5-	$C_{20}H_{20}N_2O_3S$	368	289	44	7.60	7.67	0.55	S2
8b	2-Cl-C_6H_4-	$C_{20}H_{19}ClN_2O_3S$	403	245	47	6.95	6.94	0.48	S2
8c	3-Cl-C_6H_4-	$C_{20}H_{19}ClN_2O_3S$	403	247	42	6.95	6.93	0.51	S2
8d	4-F-C_6H_4-	$C_{20}H_{19}FN_2O_3S$	386	287	40	7.25	7.24	0.45	S1
8e	2-NO_2-C_6H_4-	$C_{20}H_{19}N_3O_5S$	413	269	39	10.16	10.15	0.52	S1
8f	3-NO_2-C_6H_4-	$C_{20}H_{19}N_3O_5S$	413	247	47	10.16	10.14	0.55	S2
8g	4-OCH_3-C_6H_4-	$C_{21}H_{22}N_2O_4S$	398	225	41	7.03	7.02	0.32	S2
8h	2,5-$(OCH_3)_2$-C_6H_3-	$C_{22}H_{24}N_2O_5S$	428	301	44	6.54	6.53	0.59	S1
8i	2-OH-C_6H_4-	$C_{20}H_{20}N_2O_4S$	384	256	47	7.29	7.27	0.48	S1
8j	4-OH -C_6H_4-	$C_{20}H_{20}N_2O_4S$	384	214	35	7.29	7.28	0.44	S1
8k	2-OH,4-OCH_3 -C_6H_3-	$C_{21}H_{22}N_2O_5S$	414	287	52	6.76	6.75	0.51	S2
8l	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{25}N_3O_3S$	411	298	56	10.21	10.20	0.43	S2

S1 Acetone:Benzene(0.5:9.5), S2 Hexane:Ethyl acetate(9:1)

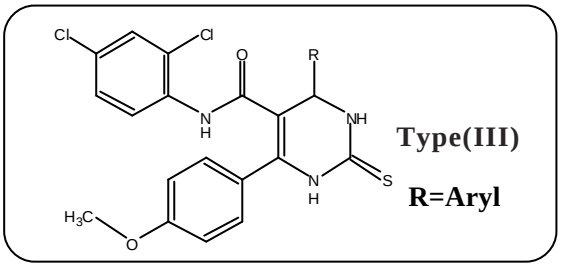
GRAPHICAL CHART NO. 8 : ANTIMICROBIAL ACTIVITY OF ETHYL-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXYLATES



SECTION - III

SYNTHESIS AND BIOLOGICAL SCREENING OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES.

Dihydropyrimidinthione derivatives have been found to be associated with various pharmacological activities. Looking to the interesting therapeutic activity, it was considered worthwhile to synthesized compounds bearing dihydropyrimidinthione moiety. Dihydropyrimidinthione derivative of type (III) have been synthesised by the condensation of N-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide with thiourea and aryl aldehydes.



Type(III)

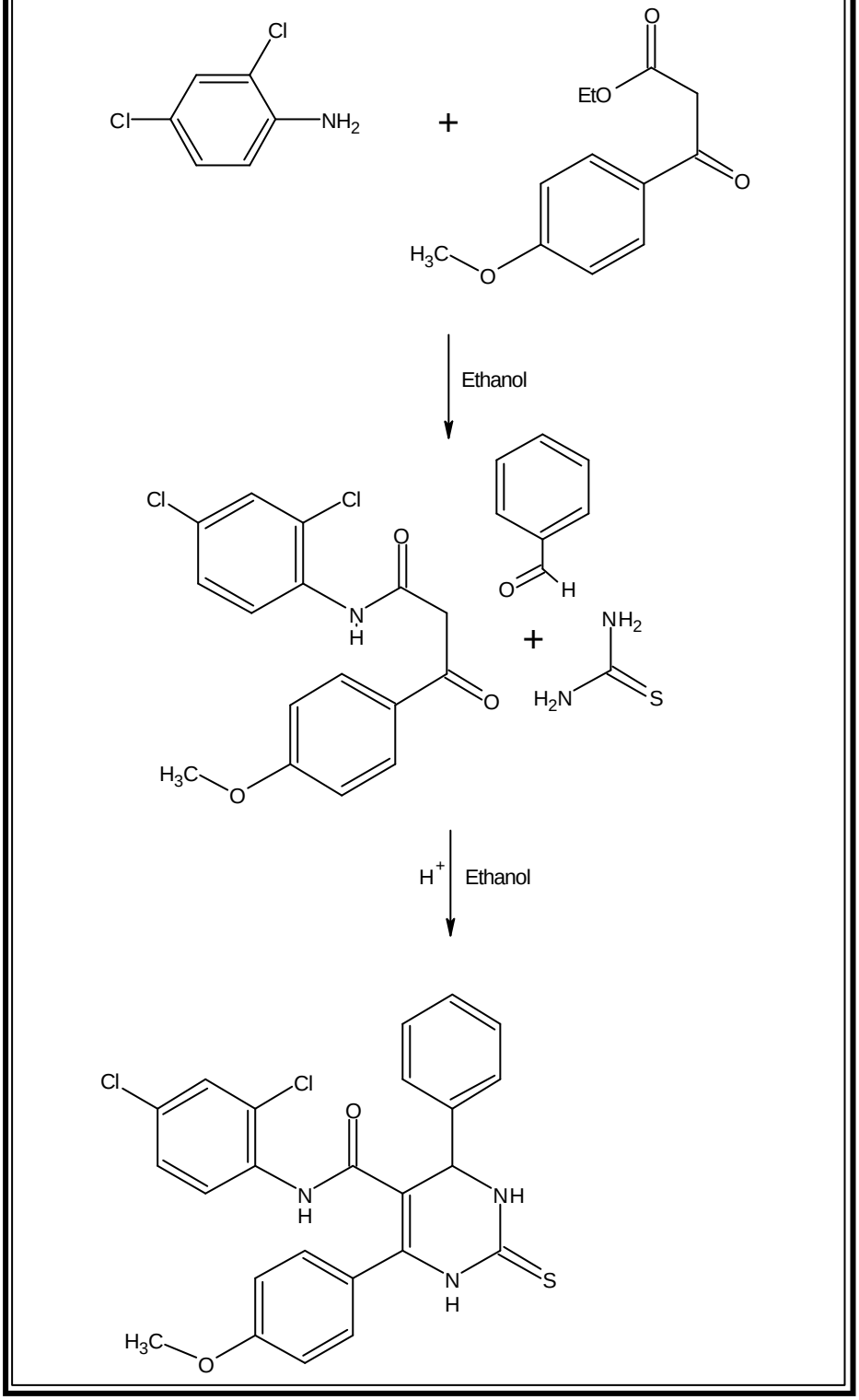
R=Aryl

The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

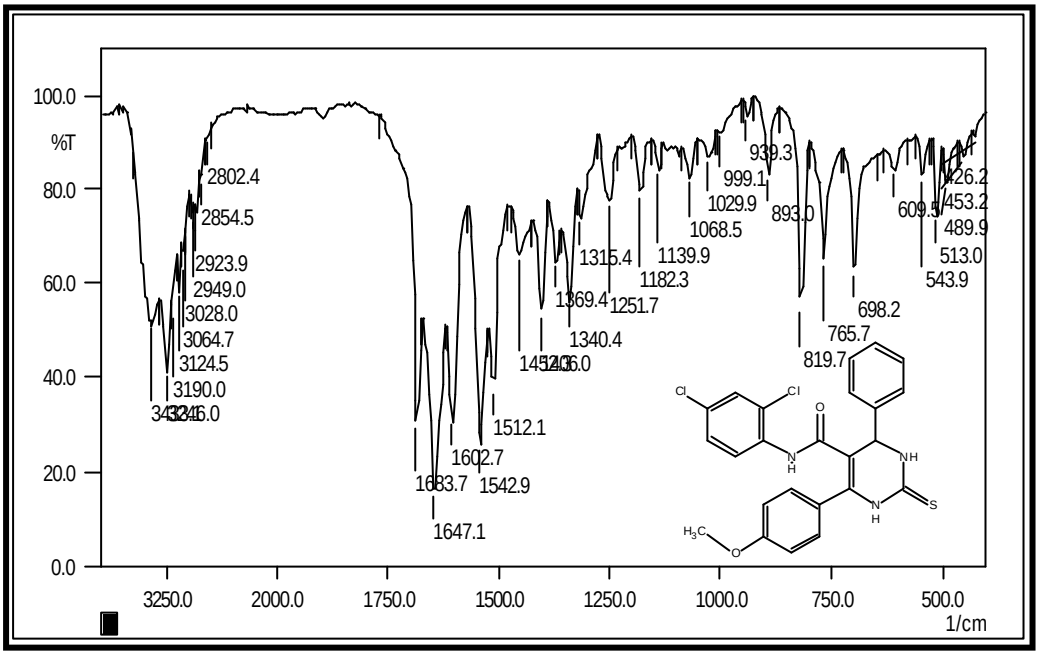
All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Moreover, some selected compounds have been evaluated for their ***in vitro*** biological assay towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at a concentration of 6.25 µg/ml using Rifampin as a standard drug which have been tested at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF), Alabama, U. S. A.

Reaction Scheme



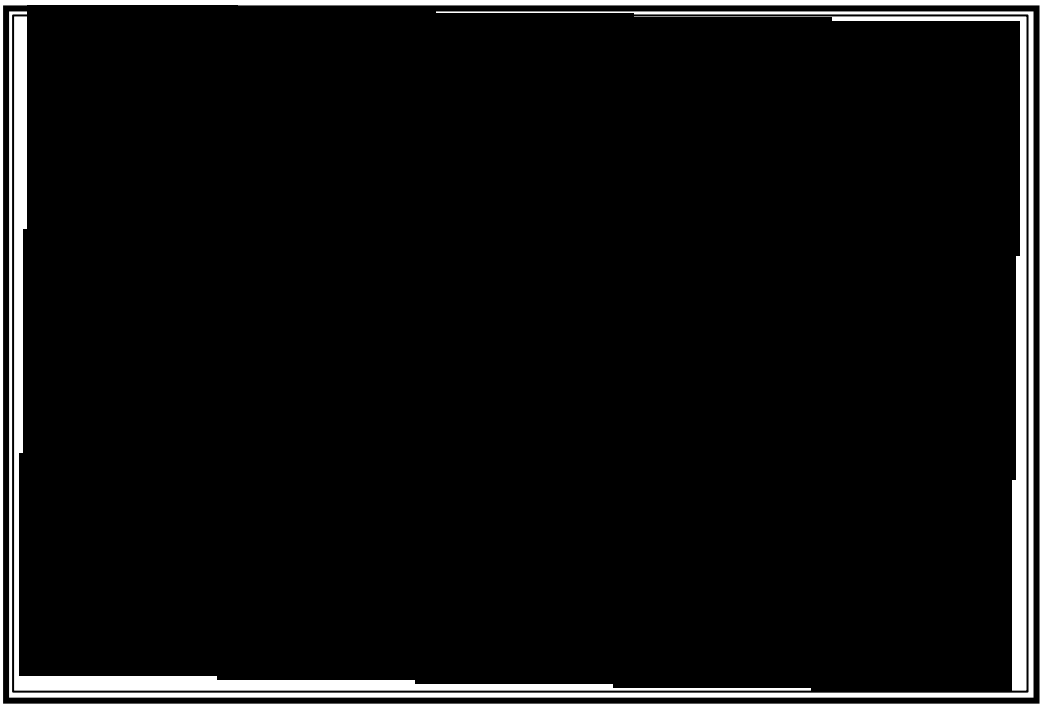
IR SPECTRAL STUDIES OF N-(2,4-DICHLOROPHENYL)-6-(4-METH OXYPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)- THIONE-5-CARBOXAMIDE.



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2923	2975-2950	126
-CH_3	C-H str. (sym.)	2854	2880-2860	,,
	C-H i.p.def. (asym.)	1452	1470-1435	,,
	C-H o.o.p. def. (sym.)	1369	1390-1370	,,
Aromatic	C-H str.	3064	3090-3030	127
	C=C str.	1406	1540-1480	,,
	C-H i.p. (def.)	1068	1125-1090	,,
	C-H o.o.p. (def)	819	835-810	,,
Pyrimidine	C=C str.	1542	1580-1520	,,
moity	C-H str.	3028	3080-3030	,,
	C-H i.p. def.	1139	1125-1090	,,
Amine	-NH str.	3432	3410-3380	126
	-NH def.	1602	1635-1595	,,
Amide	- C=O str	1683	1690-1660	,,
Halide	-C-Cl str.	765	700-750	,,

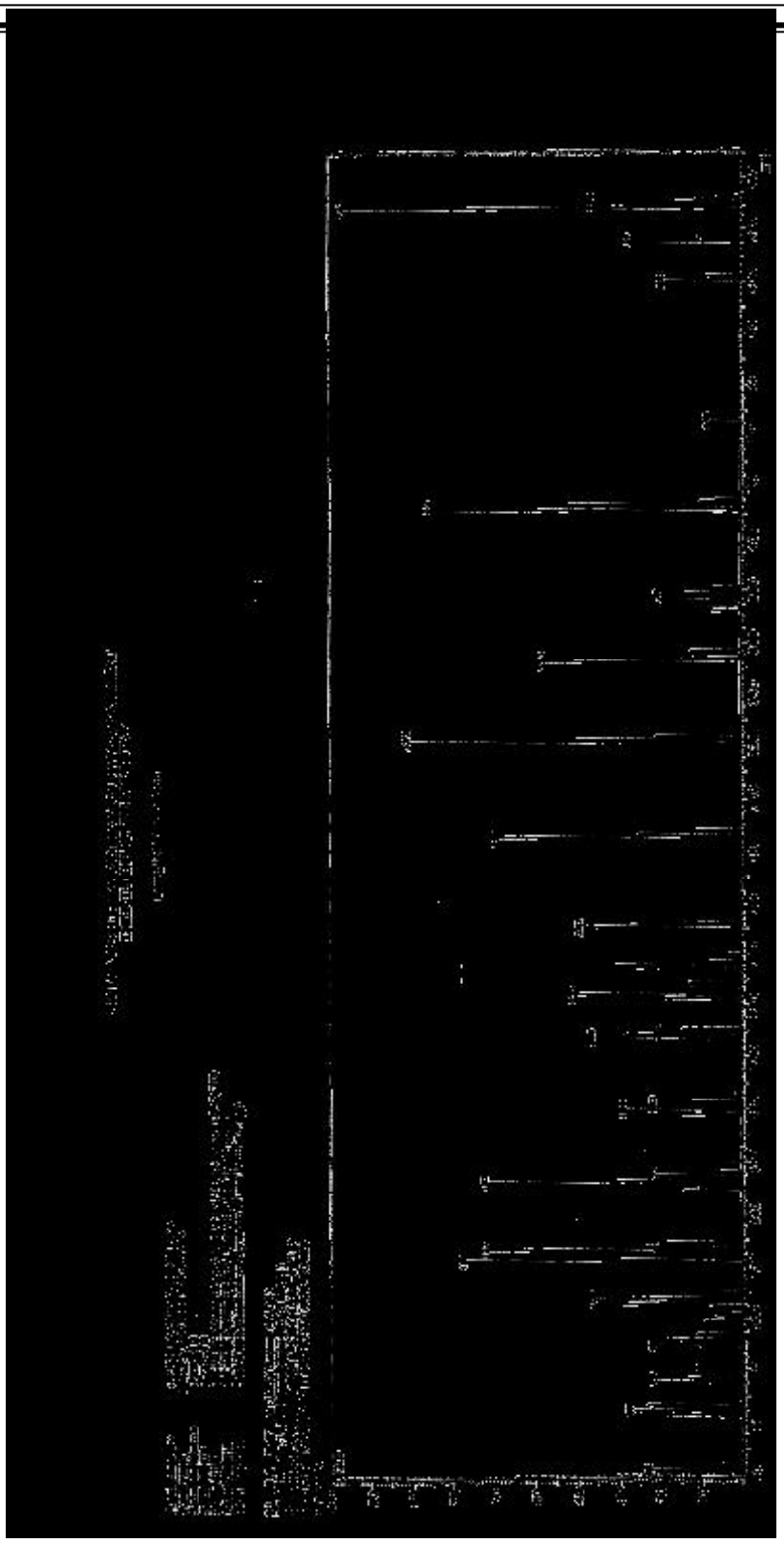
NMR SPECTRAL STUDIES OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	3.91	3H	singlet	Ar-OCH_3	-
2	5.56	1H	singlet	Ar-Hc	-
3	6.97-7.00	2H	doublet	Ar-Hb,b'	Jaa'=9.0
4	7.25-7.37	8H	multiplet	Ar-H	-
5	7.56-7.59	2H	doublet	Ar-Ha,a'	Jbb'=9.0
6	8.87	1H	singlet	-NH(Amide)	-

MASS SPECTRAL STUDIES OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-(3-NITROPHENYL)-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES.

(A) Synthesis of Synthesis of Ethyl-3-(4-methoxyphenyl)-3-oxopropanoate.

See Part-I, Section-II (A).

(B) Synthesis of N-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide.

See Part-I, Section-III (B).

(C) Synthesis of N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxamide.

A mixture of N-(2,4-dichlorophenyl)-3-(4-methoxyphenyl)-3-oxopropanamide (3.38 gm, 0.01 mol), thiourea (0.76 gm, 0.01 mol) and benzaldehyde (1.06 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^0C. The resulting solid mass separated was filtered and, crystallized from dioxane. Yield 36%, m.p.258^{0}C, Anal.Calcd. for $C_{24}H_{19}Cl_2N_3O_2S$ Calcd: C, 59.51; H, 3.95; N, 8.67%, Found: C, 59.49; H, 3.93; N, 8.66%

Similarly, other N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxamides were prepared. The physical data are recorded in Table No.9

(C) Biological screening of N-(2,4-Dichlorophenyl)-6-(4-methoxyphenyl)-4-aryl-3,4-dihydropyrimidin-2(1H)-thione-5-carboxamides.

Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.9

TABLE-9 : PHYSICAL CONSTANTS OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL- 3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
9a	C_6H_5-	$C_{24}H_{19}CI_2N_3O_2S$	484	258	36	8.67	8.66	0.54	S2
9b	2-Cl-C_6H_4-	$C_{24}H_{18}Cl_3N_3O_2S$	519	154	47	8.10	8.08	0.48	S1
9c	3-Cl-C_6H_4-	$C_{24}H_{18}Cl_3N_3O_2S$	519	245	39	8.10	8.09	0.50	S2
9d	4-Cl-C_6H_4-	$C_{24}H_{18}Cl_3N_3O_2S$	519	257	37	8.10	8.09	0.49	S1
9e	4-F-C_6H_4-	$C_{24}H_{18}Cl_2FN_3O_2S$	502	286	33	8.36	8.33	0.52	S2
9f	2-NO_2-C_6H_4-	$C_{24}H_{18}Cl_2N_4O_4S$	529	210	40	10.58	10.57	0.54	S1
9g	3-NO_2-C_6H_4-	$C_{24}H_{18}Cl_2N_4O_4S$	529	227	47	10.58	10.56	0.32	S2
9h	4-OCH_3-C_6H_4-	$C_{25}H_{21}Cl_2N_3O_3S$	514	287	49	8.17	8.17	0.50	S1
9i	2,5-$(OCH_3)_2$-C_6H_3-	$C_{26}H_{23}Cl_2N_3O_4S$	544	312	41	7.72	7.71	0.42	S1
9j	2-OH -C_6H_4-	$C_{24}H_{19}Cl_2N_3O_3S$	500	365	35	8.40	8.38	0.46	S2
9k	2-OH,4-OCH_3 -C_6H_3-	$C_{25}H_{21}Cl_2N_3O_4S$	530	327	54	7.92	7.90	0.54	S2
9l	4-$N(CH_3)_2$-C_6H_4-	$C_{26}H_{24}Cl_2N_4O_2S$	527	223	45	10.62	10.60	0.44	S1

S1 Acetone:Benzene(2:8), S2 Acetone:Benzene(1:9)

ANTITUBERCULAR ACTIVITY OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXYPHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES.

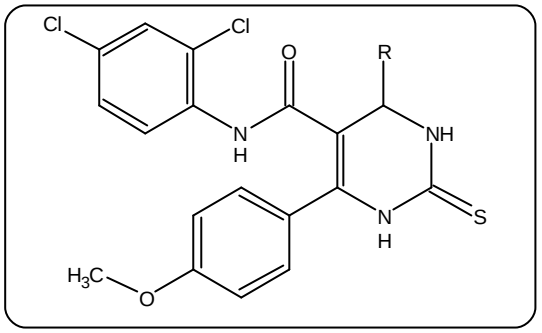


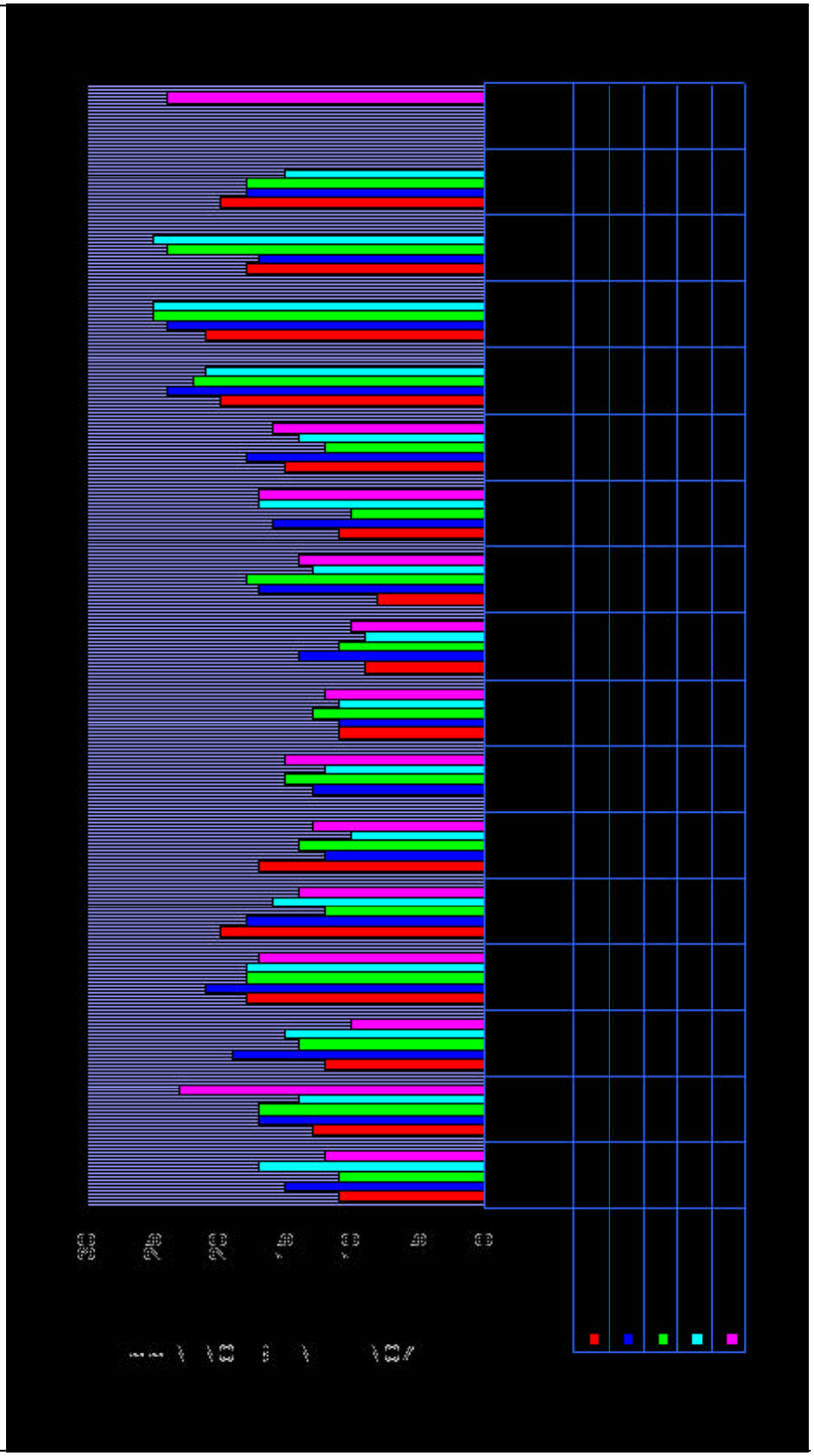
TABLE NO-9

TAACF, Southern Research Insitute

Primary Assay Summary Report

Sr. No.	Sample ID	Corp ID	R	Assay	Mtb Strain	MIC mg/ml	% Inhibi.
9a	179676	ZP-40	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	40
9b	179677	ZP-41	2-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
9c	179678	ZP-42	3-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
9d	179679	ZP-43	2-OH-4-OCH_3-C_6H_3	Alamar	$H_{37}Rv$	>6.25	52
9e	179680	ZP-44	2-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
9f	179681	ZP-45	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	18
9g	179682	ZP-46	$C_{10}H_7$-	Alamar	$H_{37}Rv$	>6.25	24
9h	179683	ZP-47	3-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	33
9i	179684	ZP-48	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	41
9j	179685	ZP-49	4-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
9k	179686	ZP-50	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
9l	179687	ZP-51	4-$N(CH_3)_2$-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	34

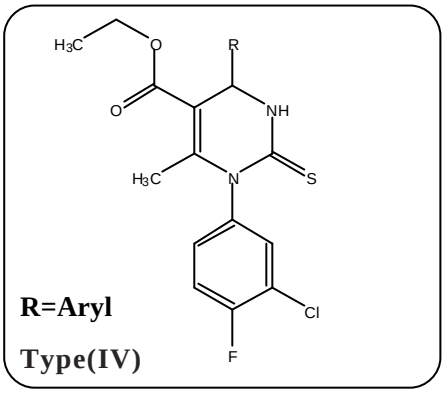
GRAPHICAL CHART NO. 9 : ANTIMICROBIAL ACTIVITY OF N-(2,4-DICHLOROPHENYL)-6-(4-METHOXY PHENYL)-4-ARYL-3,4-DIHYDROPYRIMIDIN-2(1H)-THIONE-5-CARBOXAMIDES



SECTION - IV

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES.

Dihydropyrimidinthione derivatives constitute an interesting class of comopounds because of thier varied medicinal applications. In order to explor the activities associated with the nucleus, the synthesis of dihydropyrimidinthione derivatives of type (IV) has been undertaken by the cyclocondensation ethylacetoacetate,N-(3-chloro-4-fluorophenyl)thiourea and aryl aldehydes.



R=Aryl

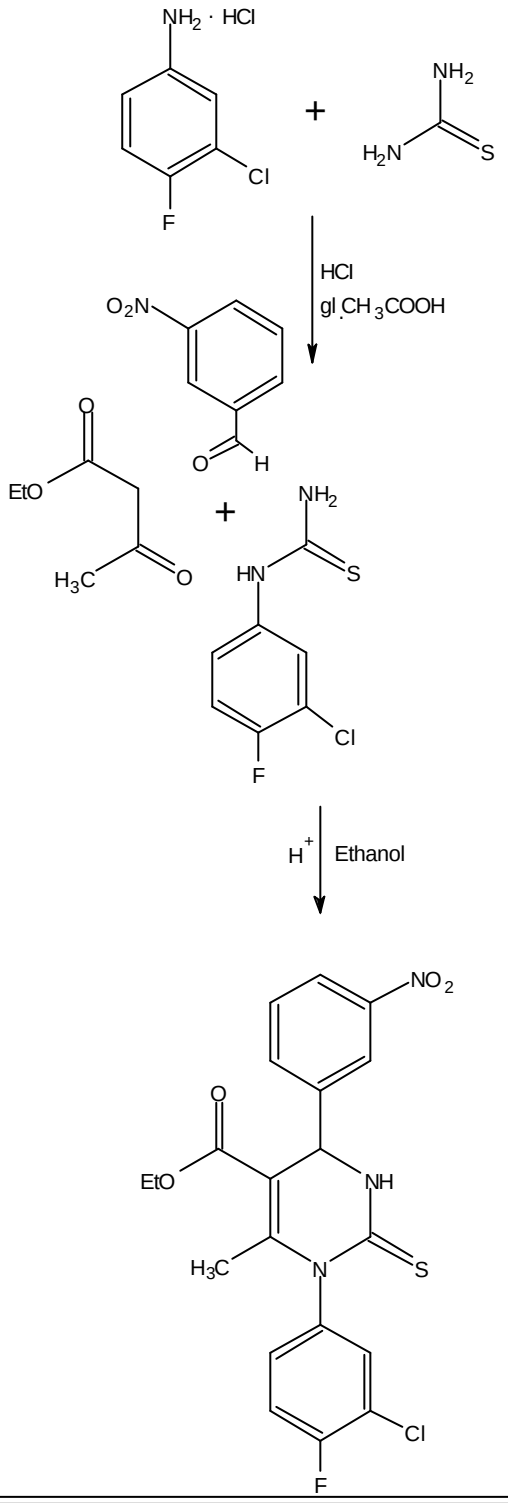
Type(IV)

The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

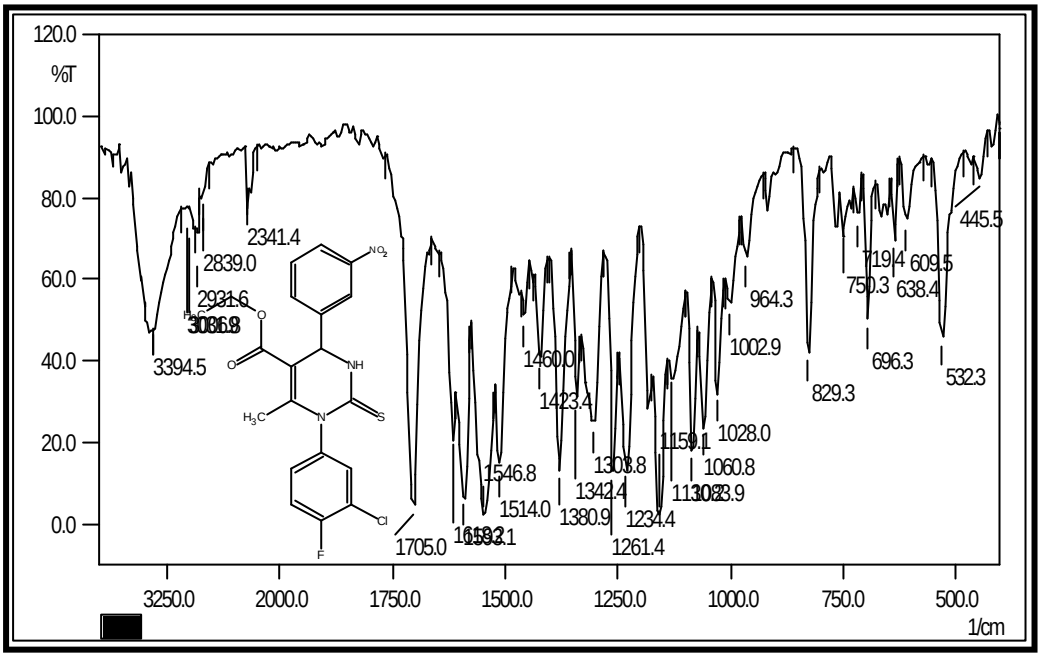
All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Moreover, some selected compounds have been evaluated for their ***in vitro*** biological assay towards a strain of ***Mycobacterium tuberculosis*** $H_{37}Rv$ at a concentration of 6.25 µg/ml using Rifampin as a standard drug which have been tested at Tuberculosis Antimicrobial Acquisition Co-ordinating Facility (TAACF), Alabama, U. S. A.

Reaction Scheme



IR SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUORO PHENYL)-4-(3-NITROPHENYL)-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-THIONE-5- CARBOXYLATE.

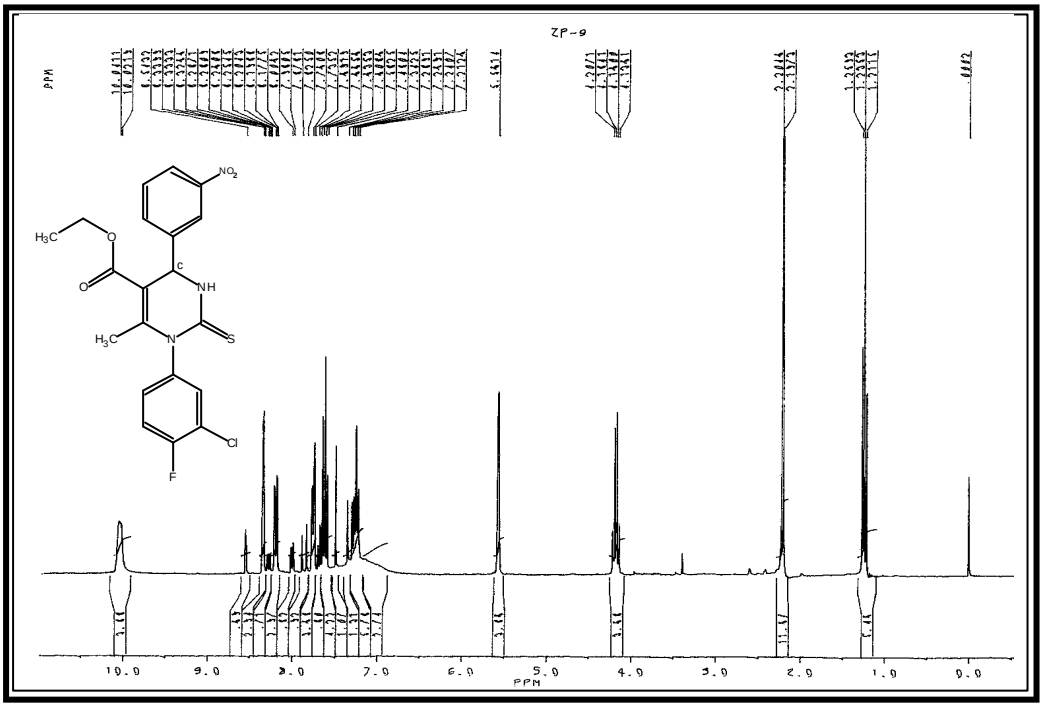


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}

(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2931	2975-2950	126
$-CH_3$	C-H str. (sym.)	2839	2880-2860	,,
	C-H i.p.def. (asym.)	1460	1470-1435	,,
	C-H o.o.p. def. (sym.)	1342	1390-1370	,,
Aromatic	C-H str.	3006	3090-3030	127
	C=C str.	1423	1540-1480	,,
	C-H i.p. (def.)	1060	1125-1090	,,
	C-H o.o.p. (def)	829	835-810	,,
Pyrimidine	C=C str.	1546	1580-1520	,,
moity	C-H str.	3031	3080-3030	,,
	C-H i.p. def.	1083	1125-1090	,,
Amine	-NH str.	3394	3410-3380	126
	-NH def.	1618	1635-1595	,,
Ester	- C=O str.	1705	1690-1660	,,
Halide	-C-CI str.	750	700-750	,,

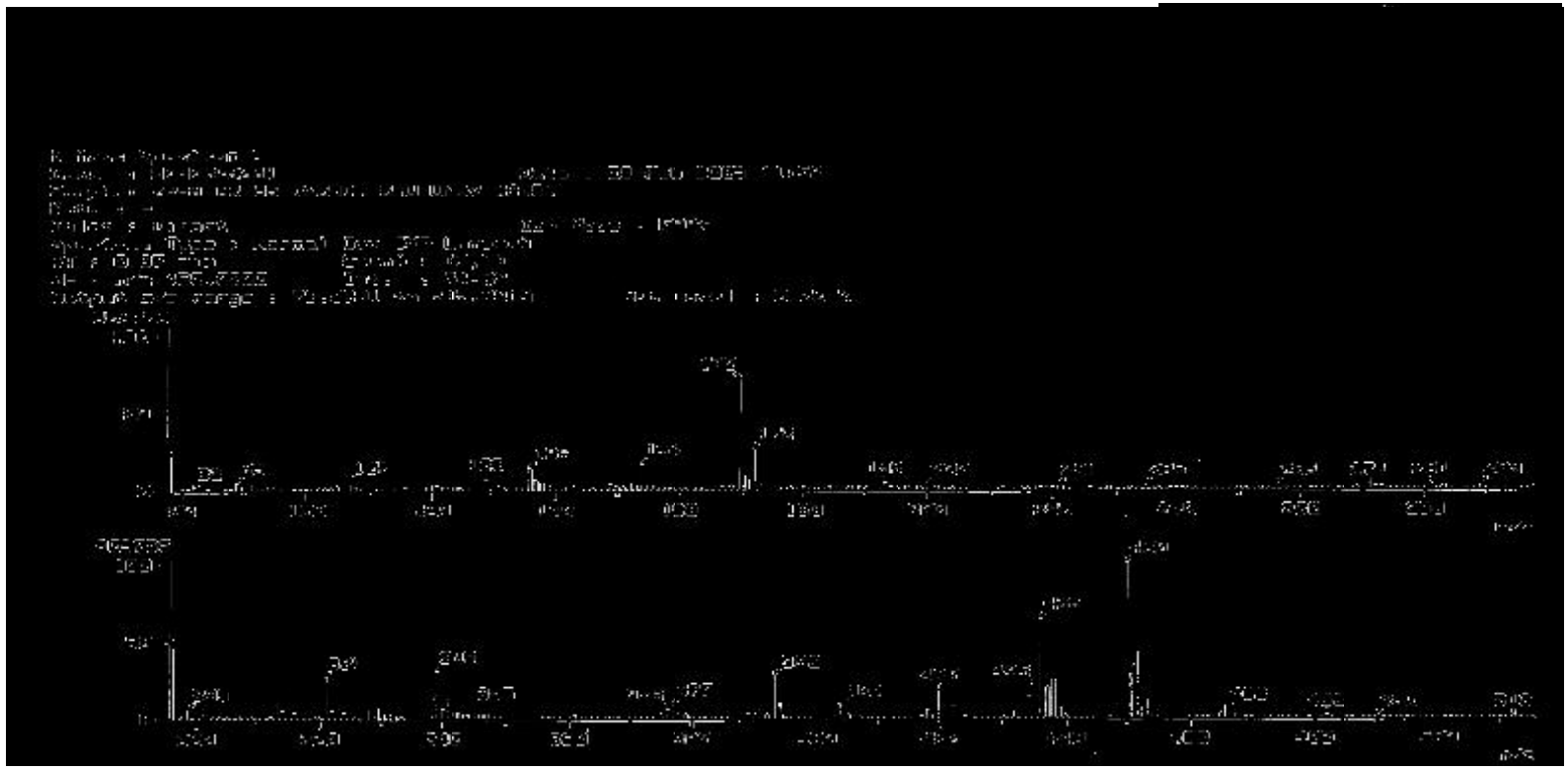
NMR SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUORO PHENYL)-4-(3-NITROPHENYL)-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-THIONE-5- CARBOXYLATE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.22	3H	triplet	$-CH_3$	-
2	2.20	3H	singlet	$Ar-CH_3$	-
3	4.76	2H	quatret	$-CH_2$	-
4	5.56	1H	singlet	Ar-Hc	-
5	7.21-8.33	7H	multiplet	Ar-H	-
6	10.04	1H	singlet	NH(Pyr.)	-

MASS SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-(3-NITROPHENYL)-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES.

(A) Synthesis of N-(3-chloro-4-fluorophenyl)thiourea.

A mixture of 3-chloro-4-fluoroaniline (1.45 gm 0.01 mol), concentrated HCI 30% (10 ml) and ammonium thiocyanate (1.52 gm 0.02 mol) in water as solvent was refluxed for 10-12 hrs. The resulting mixture was poured into ice water. Excess of hydrochloric acid and ammonium thiocyanate were removed with hot water and crude product was isolated and crystallised in methanol. Yield 89%, m.p.236 ^{0}C, Anal.Calcd. for $C_7H_6CIFN_2S$ Calcd: C, 41.04; H, 2.96; N, 13.69%, Found: C, 41.03; H, 2.95; N, 13.65%.

(B) Synthesis of Ethyl-1-(3-chloro-4-fluorophenyl)-4-(3-nitrophenyl)-6-methyl-3,4-dihydropyrimidin-2-thione-5-carboxylate.

A mixture of ethyl acetoacetate (1.30 gm, 0.01 mol), N-(3-chloro-4-fluorophenyl)thiourea (2.04 gm, 0.01 mol) and m-nitrobenzaldehyde (1.51 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O ^{0}C. The resulting solid mass separated was filtered and crystallized from dioxane. Yield 32%, m.p.269 ^{0}C, Anal.Calcd. for $C_{20}H_{17}CIFN_3O_4S$ Calcd: C, 55.39; H, 3.81; N, 9.34%, Found: C, 55.37; H, 3.80; N, 9.33%.

Similarly, other Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-thione-5-carboxylates were prepared. The physical data are recorded in Table No.10

(C) Biological screening of Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-methyl-3,4-dihydropyrimidin-2-thione-5-carboxylates.

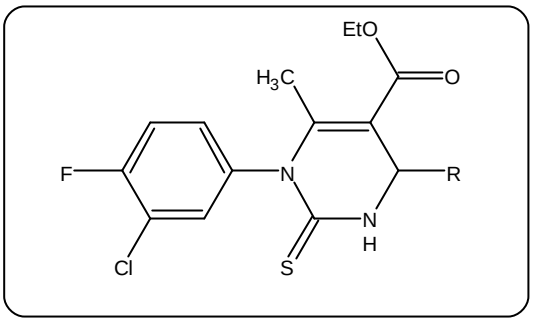
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.10

TABLE-10 : PHYSICAL CONSTANTS OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL- 3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{0}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
10a	C_6H_5-	$C_{20}H_{18}ClFN_2O_2S$	405	221	51	6.92	6.90	0.55	S2
10b	2-Cl-C_6H_4-	$C_{20}H_{17}Cl_2FN_2O_2S$	439	145	38	6.38	6.35	0.48	S2
10c	3-Cl-C_6H_4-	$C_{20}H_{17}Cl_2FN_2O_2S$	439	254	36	6.38	6.34	0.43	S1
10d	4-Cl-C_6H_4-	$C_{20}H_{17}Cl_2FN_2O_2S$	439	268	37	6.38	6.36	0.45	S1
10e	4-F-C_6H_4-	$C_{20}H_{17}ClF_2N_2O_2S$	423	254	47	6.62	6.61	0.48	S2
10f	2-NO_2-C_6H_4-	$C_{20}H_{17}ClFN_3O_4S$	450	212	34	9.34	9.32	0.56	S1
10g	3-NO_2-C_6H_4-	$C_{20}H_{17}ClFN_3O_4S$	450	269	32	9.34	9.33	0.51	S1
10h	4-OCH_3-C_6H_4-	$C_{21}H_{20}ClFN_2O_3S$	435	263	35	6.44	6.43	0.59	S2
10i	2-OH-C_6H_4-	$C_{20}H_{18}ClFN_2O_3S$	421	248	39	6.66	6.65	0.50	S2
10j	4-OH -C_6H_4-	$C_{20}H_{18}ClFN_2O_3S$	421	258	47	6.66	6.63	0.44	S1
10k	2-OH,4-OCH_3 -C_6H_3-	$C_{21}H_{20}ClFN_2O_4S$	451	247	48	6.21	6.19	0.57	S1
10l	4-$N(CH_3)_2$-C_6H_4-	$C_{22}H_{23}ClFN_3O_2S$	448	265	36	9.38	9.36	0.46	S2

S1 Hexane:Ethyl acetate(7:3), S2 Hexane:Ethyl acetate(6:4)

ANTITUBERCULAR ACTIVITY OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES.



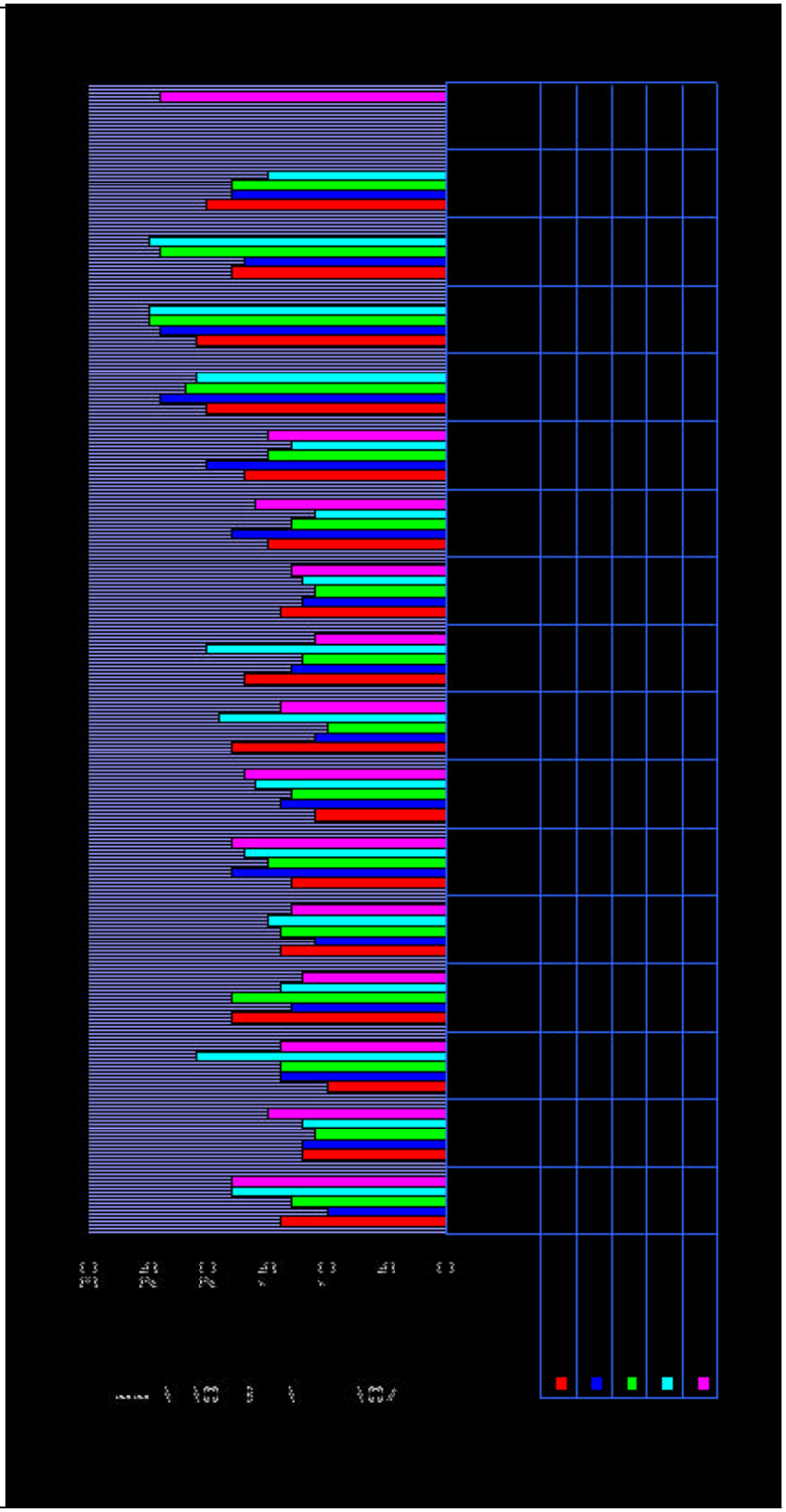
TAACF, Southern Research Insitute

TABLE NO-10

Primary Assay Summary Report

Sr. No.	Sample ID	Corp ID	R	Assay	Mtb Strain	MIC mg/ml	% Inhibi.
10a	182341	ZP-53	C_6H_5-	Alamar	$H_{37}Rv$	>6.25	45
10b	182342	ZP-54	2-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	32
10c	182343	ZP-55	3-Cl-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
10d	182344	ZP-56	3-Br-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	24
10e	182345	ZP-57	4-F-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	06
10f	182346	ZP-58	4-OCH_3-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	48
10g	182347	ZP-59	4-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
10h	182348	ZP-60	2-OH-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
10i	182349	ZP-61	2-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	51
10j	182350	ZP-62	3-NO_2-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	37
10k	182351	ZP-63	4-$N(CH_3)_2$-C_6H_4-	Alamar	$H_{37}Rv$	>6.25	00
10l	182352	ZP-64	2-OH-4-OCH_3-C_6H_3	Alamar	$H_{37}Rv$	>6.25	00

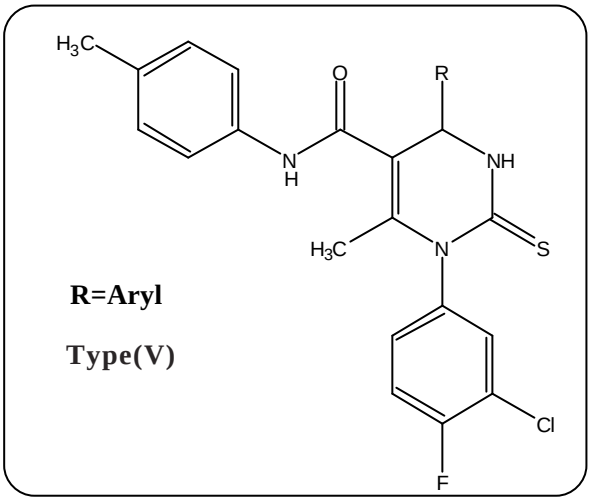
GRAPHICAL CHART NO. 10 : ANTIMICROBIAL ACTIVITYS OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES



SECTION - V

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXAMIDES.

Looking to the intresting pharmacological and agriculture activity of pyrimidine ring system, it was considered worthwhile to synthesized some new dihydropyrimidinthione derivatives of type (VIII) to study their biological activities. Dihydropyrimidinthione derivatives of type (VIII) have been prepared by the reaction of the N-(4-methylphenyl)-3-oxobutanamide,N-(3-chloro-4-fluorophenyl)thiourea and aryl aldehydes



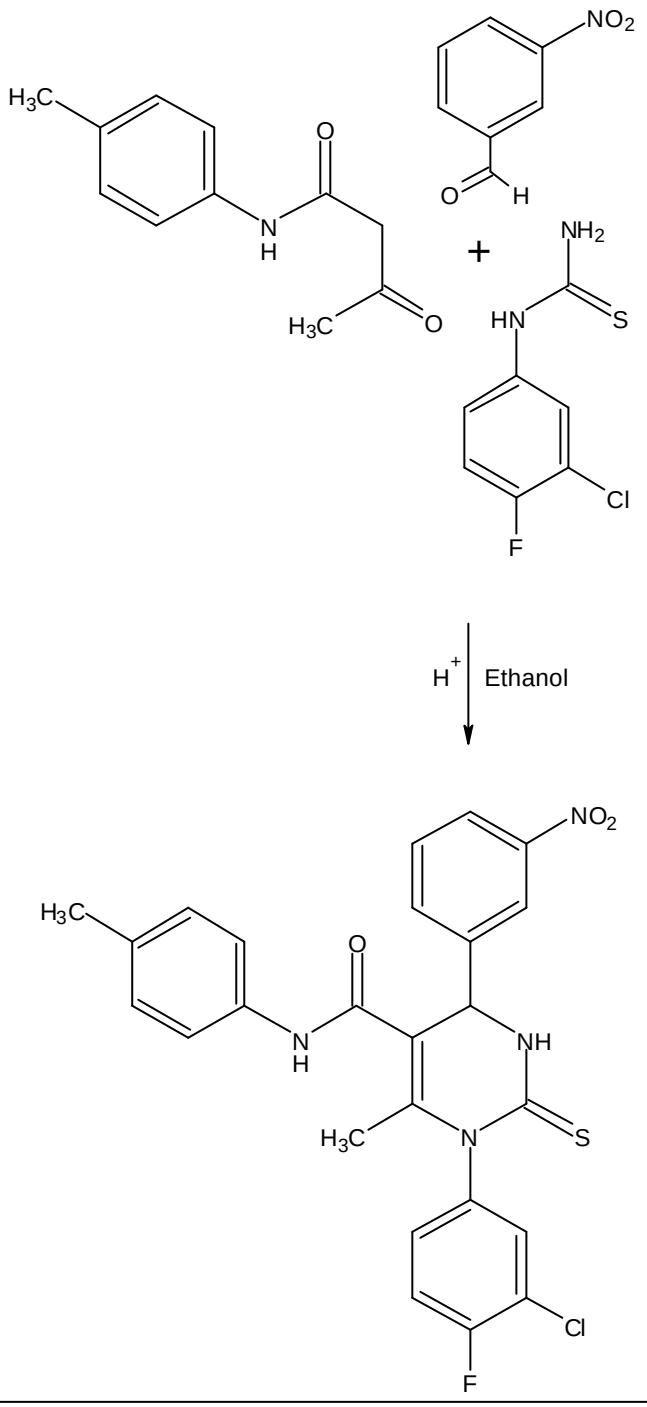
R=Aryl

Type(V)

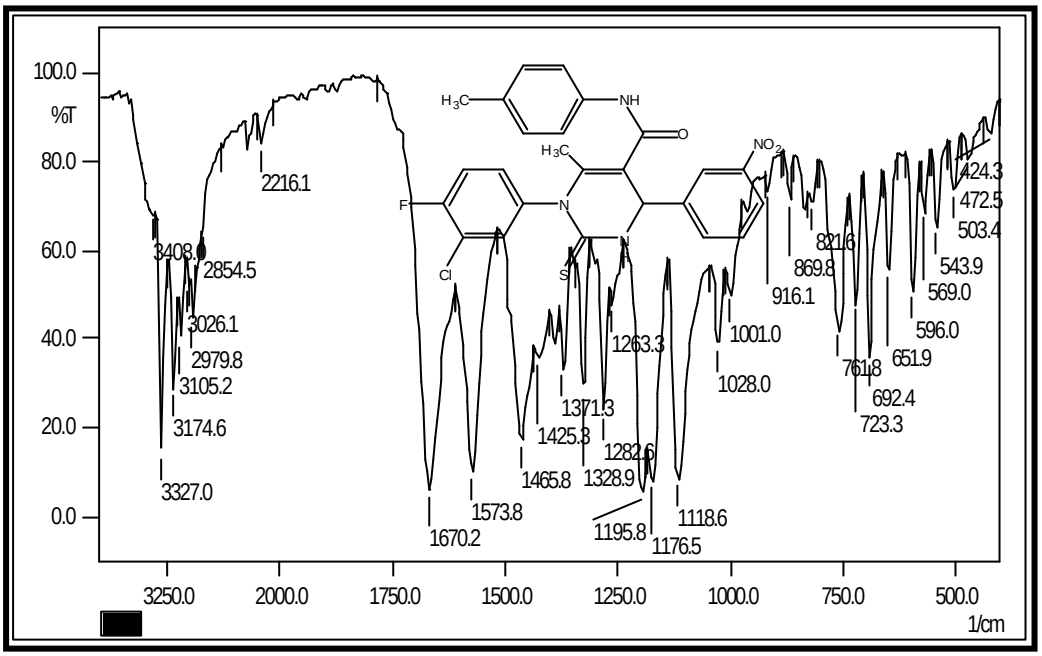
The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Reaction Scheme



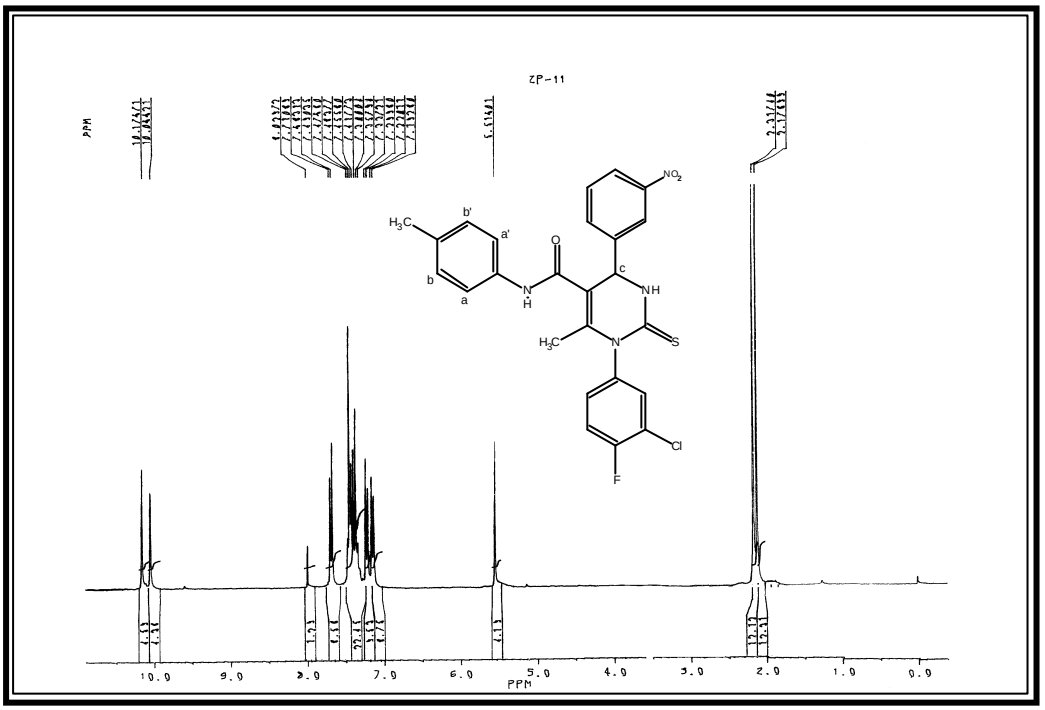
IR SPECTRAL STUDIES OF 1-(3-CHLORO-4-FLUORPHENYL)-4-(3-NITROPHENYL)-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDRO PYRIMIDIN-2-THIONE-5-CARBOXAMIDE.



Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1} (KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2979	2975-2950	126
-CH_3	C-H str. (sym.)	2854	2880-2860	,,
	C-H i.p.def. (asym.)	1425	1470-1435	,,
	C-H o.o.p. def. (sym.)	1328	1390-1370	,,
Aromatic	C-H str.	3105	3090-3030	127
	C=C str.	1465	1540-1480	,,
	C-H i.p. (def.)	1118	1125-1090	,,
	C-H o.o.p. (def)	821	835-810	,,
Pyrimidine	C=C str.	1542	1580-1520	,,
moity	C-H str.	3026	3080-3030	,,
	C-H i.p. def.	1139	1125-1090	,,
Amine	-NH str.	3408	3410-3380	126
	-NH def.	1573	1635-1595	,,
Amide	- C=O str.	1670	1690-1660	,,
Halide	-C-Cl str.	761	700-750	,,

NMR SPECTRAL STUDIES OF 1-(3-CHLORO-4-FLUORPHENYL)-4-(3-NITROPHENYL)-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDRO PYRIMIDIN-2-THIONE-5-CARBOXAMIDE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	2.17	3H	singlet	-CH_3(Pyr.)	-
2	2.31	3H	singlet	Ar-CH_3	-
3	5.51	1H	singlet	Ar-Hc	-
4	7.19-7.22	2H	doublet	Ar-Ha,a'	Jaa'=9.0
5	7.29-7.49	7H	multiplate	Ar-H	-
6	7.68-7.71	2H	doublet	Ar-Hb,b'	Jbb'=9.0
7	10.06	1H	singlet	-NH(Amide)	-
8	10.17	1H	singlet	-NH(Pyr.)	-

MASS SPECTRAL STUDIES OF 1-(3-CHLORO-4-FLUORPHENYL)-4-PHENYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXAMIDE.

EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXAMIDES.

(A) Synthesis of N-(4-methylphenyl)-3-oxobutanamide.

See Part-I, Section-I (A).

(B) Synthesis of N-(3-chloro-4-fluorophenyl)thiourea.

See Part-I, Section-IV (A).

(C) Synthesis of 1-(3-Chloro-4-fluorophenyl)-4-(3-nitrophenyl)-6-methyl-N-(4-methylphenyl)-3,4-dihydropyrimidin-2-thione-5-carboxamide.

A mixture of N-(4-methyl phenyl)-3-oxobutanmide (1.91 gm, 0.01 mol), N-(3-chloro-4-fluorophenyl)thiourea (2.04 gm, 0.01 mol) and m-nitrobenzaldehyde (1.51 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^0C. The resulting solid mass separated was filtered and crystallized from dioxane. Yield 48%, m.p.214^{0}C, Anal.Calcd. for $C_{25}H_{20}ClFN_4O_3S$ Calcd: C, 58.76; H, 3.95; N, 10.96%, Found: C, 58.75; H, 3.93; N, 10.94%.

Similarly, other 1-(3-Chloro-4-fluorophenyl)-4-aryl-6-methyl-N-(4-methylphenyl)-3,4-dihydropyrimidin-2-thione-5-carboxamides were prepared. The physical data are recorded in Table No.11

(D) Biological screening of 1-(3-Chloro-4-fluorophenyl)-4-aryl-6-methyl-N-(4-methylphenyl)-3,4-dihydropyrimidin-2-thione-5-carboxamides.

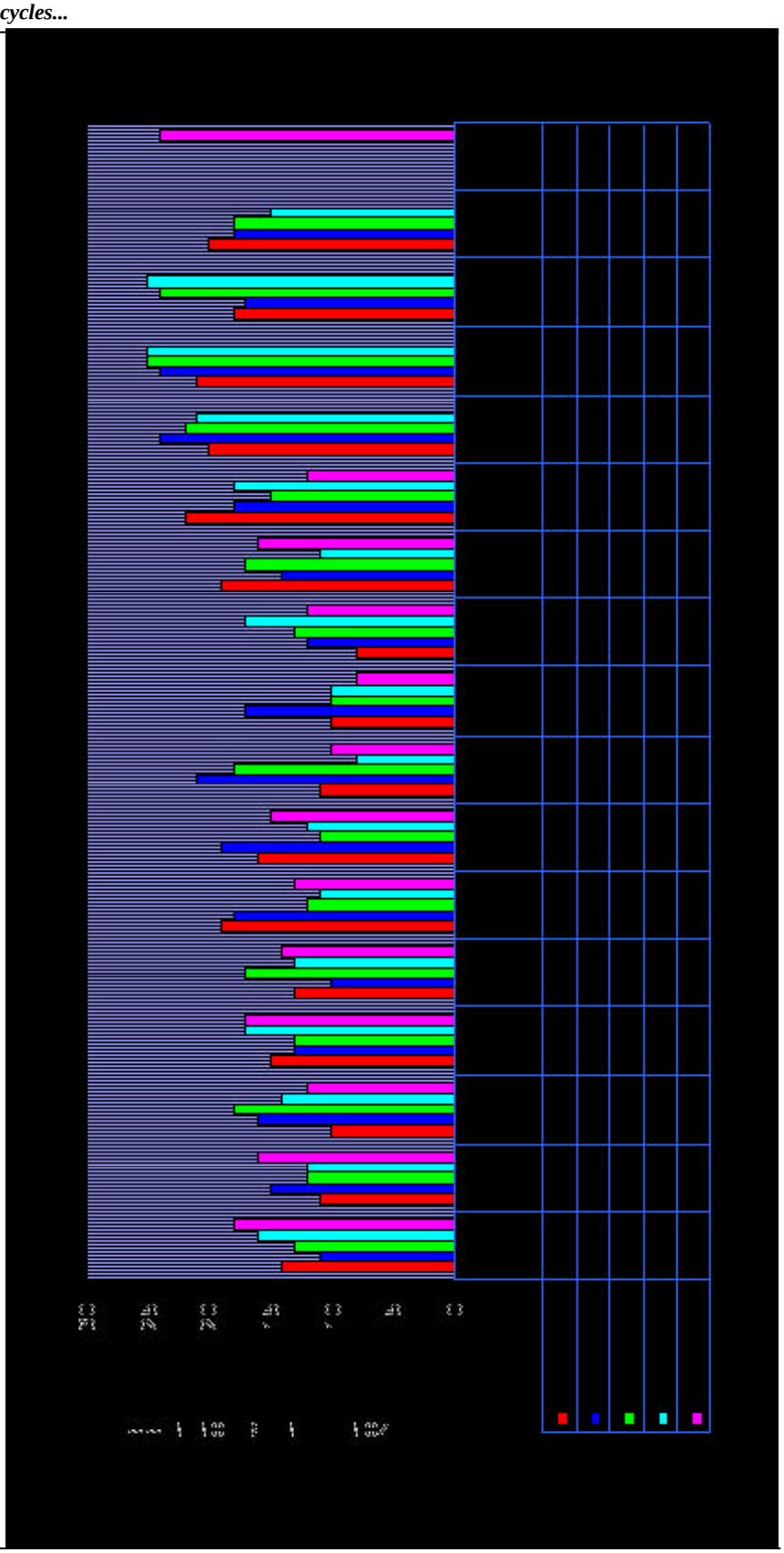
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.11

TABLE-11 :PHYSICAL CONSTANTS OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXAMIDES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
11a	C_6H_5-	$C_{25}H_{21}ClFN_3OS$	466	302	52	9.02	9.00	0.46	S2
11b	2-Cl-C_6H_4-	$C_{25}H_{20}Cl_2FN_3OS$	500	256	36	8.40	8.38	0.51	S2
11c	3-Cl-C_6H_4-	$C_{25}H_{20}Cl_2FN_3OS$	500	236	47	8.40	8.39	0.49	S1
11d	4-Cl-C_6H_4-	$C_{25}H_{20}Cl_2FN_3OS$	500	287	48	8.40	8.37	0.54	S2
11e	2-NO_2-C_6H_4-	$C_{25}H_{20}ClFN_4O_3S$	511	269	36	10.96	10.95	0.46	S1
11f	3-NO_2-C_6H_4-	$C_{25}H_{20}ClFN_4O_3S$	511	214	48	10.96	10.94	0.56	S2
11g	2-OH-C_6H_4-	$C_{25}H_{21}ClFN_3O_2S$	482	235	41	8.72	8.69	0.47	S2
11h	2-OH,4-OCH_3 -C_6H_3-	$C_{26}H_{23}ClFN_3O_3S$	512	237	47	8.21	8.18	0.59	S1
11i	4-F-C_6H_4-	$C_{25}H_{20}ClF_2N_3OS$	484	301	42	8.68	8.65	0.38	S1
11j	4-OCH_3 -C_6H_4-	$C_{26}H_{23}ClFN_3O_2S$	496	332	50	8.47	8.45	0.44	S1
11k	2,5-$(OCH_3)_2$-C_6H_3-	$C_{27}H_{25}ClFN_3O_3S$	526	254	48	7.99	7.95	0.49	S2
11l	3-C_6H_5-O-C_6H_4-	$C_{31}H_{25}ClFN_3O_2S$	558	287	57	7.53	7.51	0.43	S2

S1 Hexane:Ethyl acetate(6:4), S2 Hexane:Ethyl acetate(8:2)

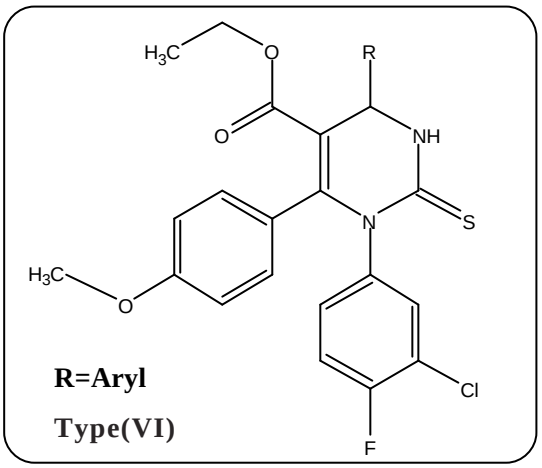
GRAPHICAL CHART NO. 11 : ANTIMICROBIAL ACTIVITY OF 1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-METHYL-N-(4-METHYLPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXAMIDES



SECTION - VI

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES.

Dihydroyrimidinthiones have been studied extensively because of their ready accessibility, diverse chemical reactivity and broad spectrum of biological activities. Led by these considerations the synthesis of pyrimidine derivatives of type (VI) has been undertaken by the cyclocondensation of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate, N-(3-chloro-4-fluorophenyl)thiourea and aryl aldehydes.



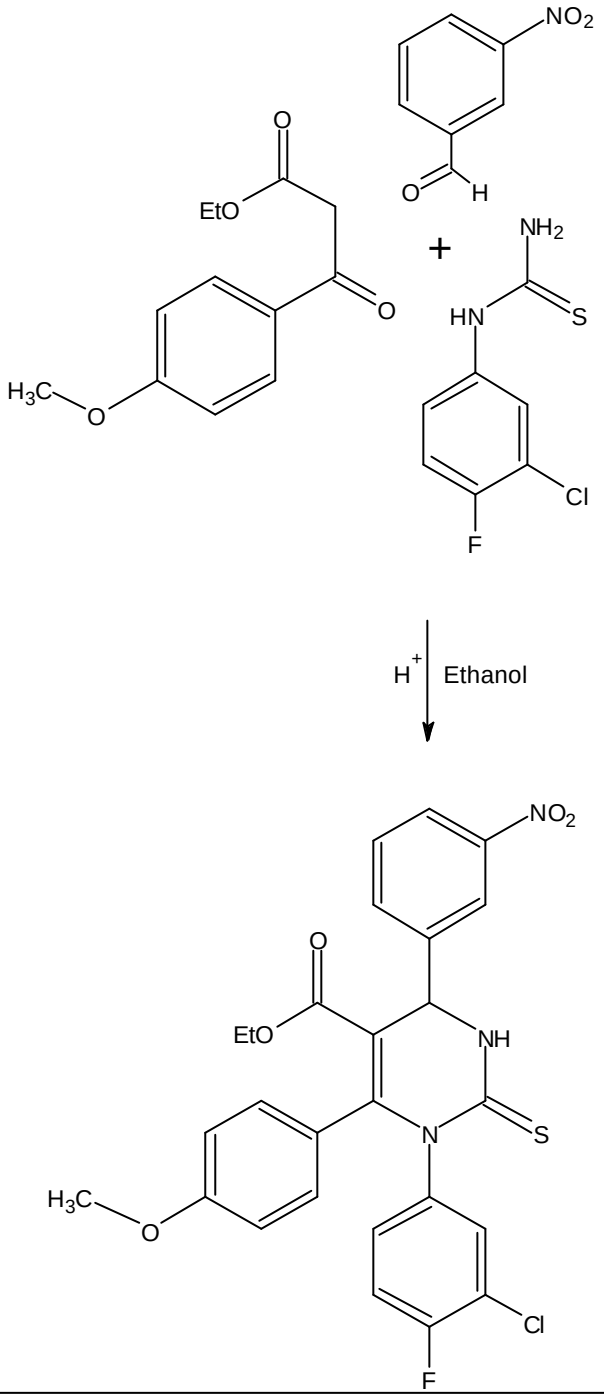
R=Aryl

Type(VI)

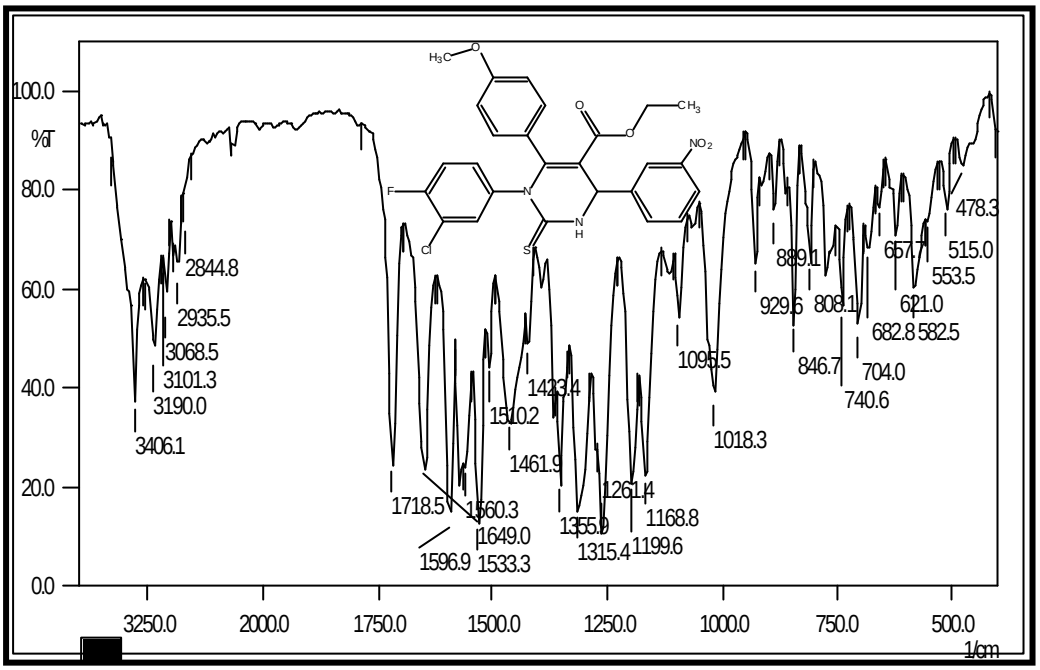
The structure elucidation of synthesized compounds has been done on the basis of elemental analyses, infrared and ^{1}H nuclear magnetic resonance spectroscopy and further supported by Mass spectrometry.

All the compounds have been evaluated for their ***in vitro*** biological assay like antibacterial activity towards gram positive and gram negative bacterial strains and antifungal activity towards ***Aspergillus niger*** at a concentration of 40µg/ml. The biological activities of synthesized compounds were compared with standard drugs.

Reaction Scheme



IR SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUORO PHENYL)-4-(3-NITROPHENYL)-6-(METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATE.

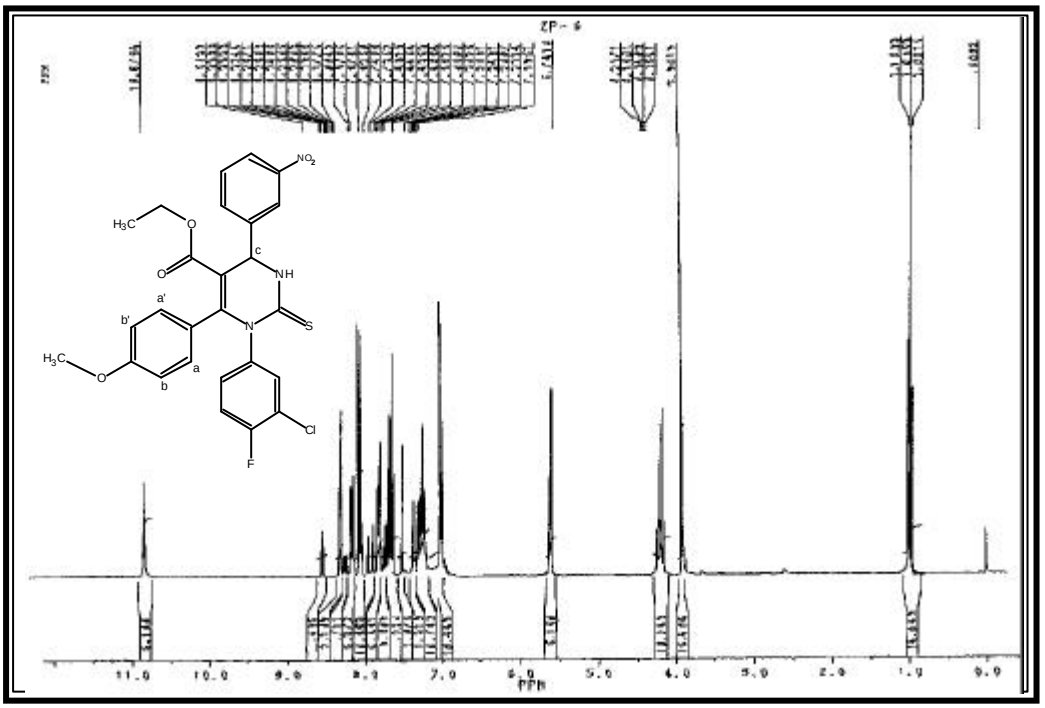


Instrument : SHIMADZU FTIR 8400 Spectrophotometer; Frequency range: 4000-400 cm^{-1}

(KBr disc.)

Type	Vibration Mode	Frequency in cm-1		Ref.
		Observed	Reported	
Alkane	C-H str. (asym.)	2935	2975-2950	126
$-CH_3$	C-H str. (sym.)	2844	2880-2860	,,
	C-H i.p.def. (asym.)	1461	1470-1435	,,
	C-H o.o.p. def. (sym.)	1355	1390-1370	,,
Aromatic	C-H str.	3051	3090-3030	127
	C=C str.	1423	1540-1480	,,
	C-H i.p. (def.)	1095	1125-1090	,,
	C-H o.o.p. (def)	808	835-810	,,
Pyrimidine	C=C str.	1560	1580-1520	,,
moity	C-H str.	3101	3080-3030	,,
	C-H i.p. def.	1168	1125-1090	,,
Amine	-NH str.	3406	3410-3380	126
	-NH def.	1649	1635-1595	,,
Ester	- C=O str.	1718	1690-1660	,,
Halide	-C-CI str.	740	700-750	,,

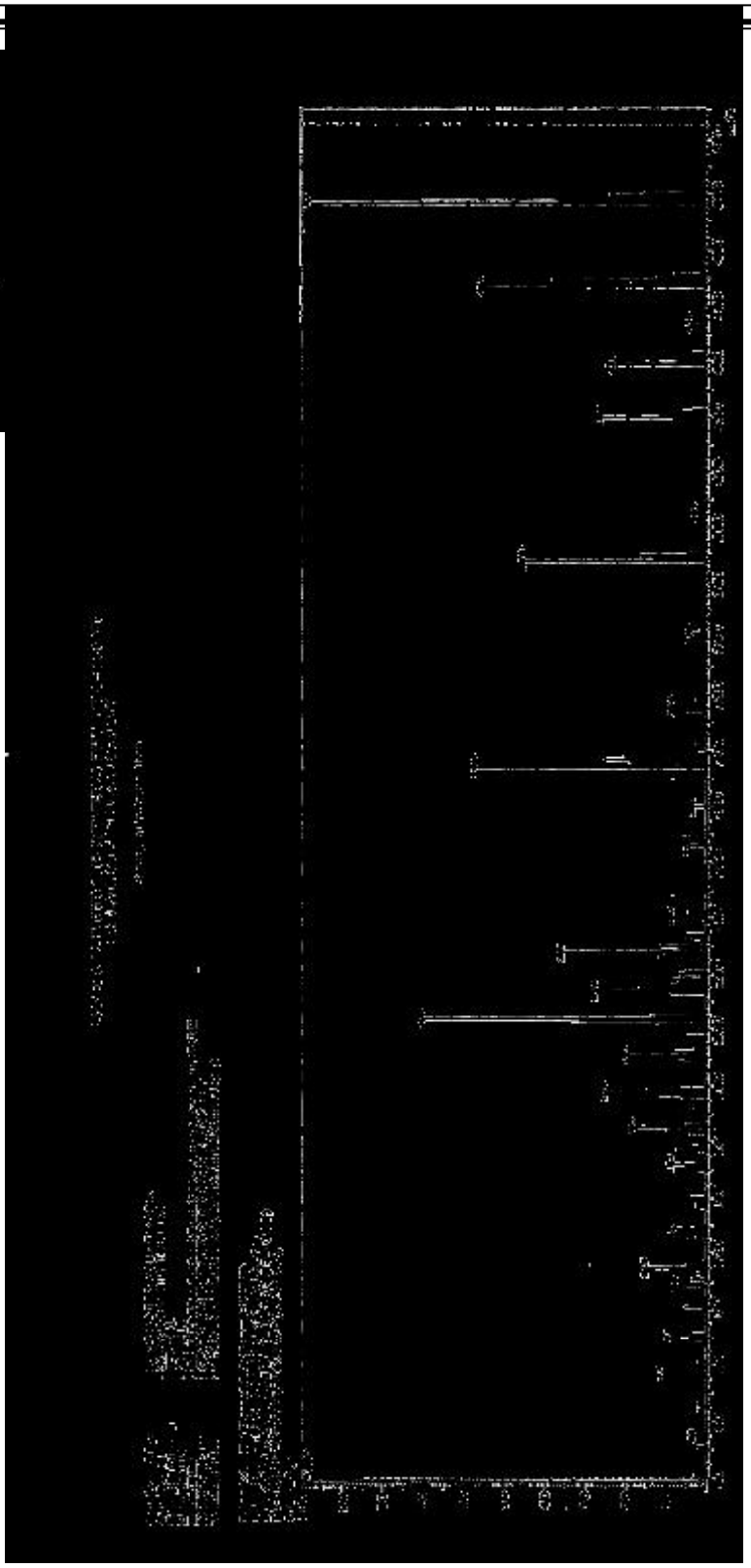
NMR SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUORO PHENYL)-4-(3-NITROPHENYL)-6-(METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATE.



Internal Standard : TMS; Solvent : $CDCl_3$: Instrument : BRUKER Spectrometer (300 MHz)

Signal No.	Signal Position (dppm)	Relative No. of protons	Multiplicity	Inference	J Value In Hz
1	1.09	3H	triplet	$-CH_3$	-
2	3.90	3H	singlet	$Ar-OCH_3$	-
3	4.76	2H	quatret	$-CH_2$	-
4	5.76	1H	singlet	Ar-Hc	-
5	7.21-7.24	2H	doublet	Ar-Hb,b'	Jaa'=9.0
6	7.24-8.34	7H	multiplet	Ar-H	
7	7.97-8.00	2H	doublet	Ar-Ha,a'	Jbb'=9.0
8	10.07	1H	singlet	NH(Pyr.)	-

MASS SPECTRAL STUDIES OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-PHENYL-6-(METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATE.



EXPERIMENTAL

SYNTHESIS AND BIOLOGICAL SCREENING OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES.

(A) Synthesis of Ethyl-3-(4-methoxyphenyl)-3-oxopropanoate.

See Part-I, Section-II (A).

(B) Synthesis of N-(3-chloro-4-fluorophenyl)thiourea.

See Part-I, Section-IV (A).

(B) Synthesis of Ethyl-1-(3-chloro-4-fluorophenyl)-4-(3-nitrophenyl)-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2-thione-5-carboxylate.

A mixture of ethyl-3-(4-methoxyphenyl)-3-oxopropanoate (2.22 gm, 0.01 mol), N-(3-chloro-4-fluorophenyl)thiourea (2.04 gm, 0.01 mol) and m-nitrobenzaldehyde (1.51 gm, 0.01 mol) in 15 ml of ethanol containing few drops of concentrated hydrochloric acid was refluxed for 24 hrs. The solution was allowed to stand for 12 hrs. at O^0C. The resulting solid mass separated was filtered and crystallized from dioxane. Yield 48%, m.p.273^{0}C, Anal.Calcd. for $C_{26}H_{21}ClFN_3O_5S$ Calcd: C, 57.62; H, 3.91; N, 7.75%, Found: C, 57.60; H, 3.90; N, 7.73%.

Similarly, other Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2-thione-5-carboxylates were prepared. The physical data are recorded in Table No.12

(C) Biological screening of Ethyl-1-(3-chloro-4-fluorophenyl)-4-aryl-6-(4-methoxyphenyl)-3,4-dihydropyrimidin-2-thione-5-carboxylates.

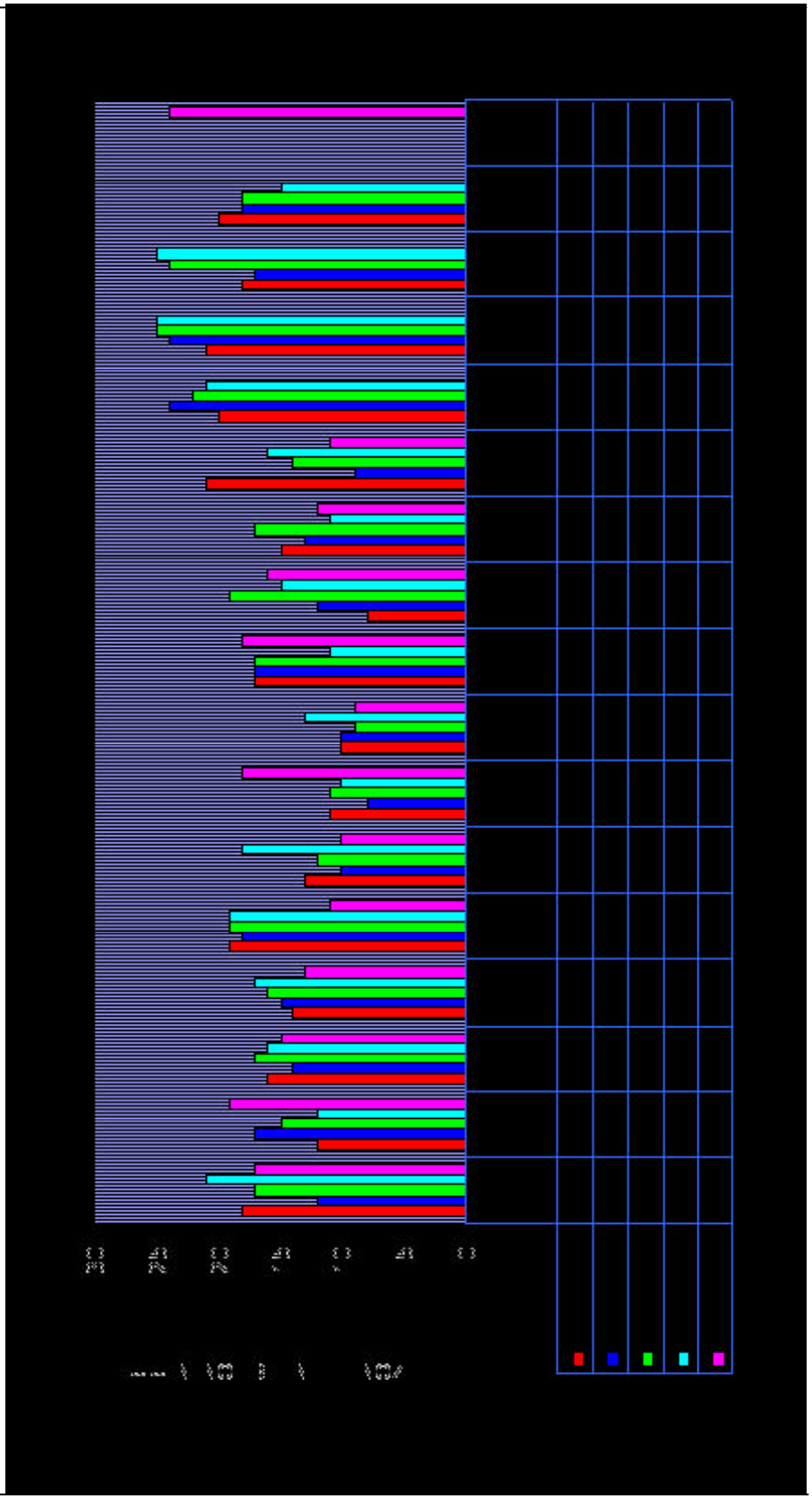
Antimicrobial testing were carried out as described in Part-I Section-I(C). The zones of inhibition of test solutions are recorded in Graphical Chart No.12

TABLE-12 : PHYSICAL CONSTANTS OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES

Sr. No	R	Molecular Formula	Molecular Weight	M.P. ^{o}C	Yield %	% of Nitrogen Calcd.	% of Nitrogen Found	Rf Value	Solvent System
1	2	3	4	5	6	7	8	9	10
12a	C_6H_5-	$C_{26}H_{22}ClFN_2O_3S$	497	242	48	5.64	5.60	0.54	S1
12b	2-Cl-C_6H_4-	$C_{26}H_{21}Cl_2FN_2O_3S$	531	189	42	5.27	5.25	0.47	S2
12c	3-Cl-C_6H_4-	$C_{26}H_{21}Cl_2FN_2O_3S$	531	258	40	5.27	5.24	0.56	S1
12d	4-Cl-C_6H_4-	$C_{26}H_{21}Cl_2FN_2O_3S$	531	254	36	5.27	5.25	0.44	S2
12e	4-F-C_6H_4-	$C_{26}H_{21}ClF_2N_2O_3S$	515	147	49	5.44	5.42	0.52	S2
12f	4-OCH_3 -C_6H_4-	$C_{27}H_{24}ClFN_2O_4S$	527	288	51	5.32	5.30	0.58	S1
12g	2,5-$(OCH_3)_2$-C_6H_3-	$C_{28}H_{26}ClFN_2O_5S$	557	236	35	5.03	5.01	0.42	S2
12h	2-NO_2-C_6H_4-	$C_{26}H_{21}ClFN_3O_5S$	542	242	31	7.75	7.74	0.58	S1
12i	3-NO_2-C_6H_4-	$C_{26}H_{21}ClFN_3O_5S$	542	273	48	7.75	7.73	0.44	S2
12j	2-OH,4-OCH_3 -C_6H_3-	$C_{27}H_{24}ClFN_2O_5S$	543	302	39	5.16	5.15	0.42	S2
12k	4-OH -C_6H_4-	$C_{26}H_{22}ClFN_2O_4S$	513	248	58	5.46	5.41	0.55	S2
12l	4-$N(CH_3)_2$-C_6H_4-	$C_{28}H_{27}ClFN_3O_3S$	540	298	48	7.78	7.72	0.44	S1

S1 Hexane:Ethyl acetate(5:5), S2 Acetone:Benzene(1:9)

GRAPHICAL CHART NO. 12 : ANTIMICROBIAL ACTIVITY OF ETHYL-1-(3-CHLORO-4-FLUOROPHENYL)-4-ARYL-6-(4-METHOXYPHENYL)-3,4-DIHYDROPYRIMIDIN-2-THIONE-5-CARBOXYLATES



REFERENCES :

1 Astwood E. B.

J. Am. Med. Assoe. **122,** 78 (1943).

2 Mc gavak; Bull N. V.; Pearson S.

Med. Coll. **16,** 58 (1953).

3 Salehi Peyman; Dabiri Minoo; Zolfigol Mohammad Ali; Bodughai Fard.

Tetrahedron Letters., **44(14)** 2889-2891 (2003).*Chem. Abstr.,* **139,** 85298 (2003).

4 Foroughifar N.; Mobinikhaledi A.;Jirandehi H. Fathinejad.

Phosphorus. Sulfur and Silicon and the related elements., **178(3),** 495-500 (2003).

Chem. Abstr., **139,** 164767 (2003).

5 Fu Nan-Yan; Yang Yao-Fang; Pang Mei-Li; Wang Ji-Tao.

Gaodeng Xuexiao Huaxae Xuebao., **24(1),** 79-81 (2003).

Chem. Abstr., **139,** 197444 (2003).

6 Cao Znong; Wang Shan-Wei; Fu Nan-Yan; Yang Yao-Fang; Wang Ji-Tao.

Tetrahedron., **58(24),** 4801-4807 (2002).

7 Subhas D. Bose; Liyakat Fatims; Hari Babu.

J. Org. Chem., **68,** 587-590 (2003).

8 Ranu C.; Alakananda Hajra; Umasish Jana.

J. Org. Chem., **65,** 6270- 6272 (2000).

9 Ranu C.; Alakananda Hajra;Suvendu S. Dey.

Organic Process Research and Development., **6(6),** 817-818 (2002).

10 Wang L.; Qian C.; Tian He; Ma Yan.

Synthetic Communications. **33(9),** 1459 (2003).

11 Stadler A.; Kappe C. O.

J. Comb. Chem. **3,** 624 (2001).

12 Dondoni A.; Massi A.; Subatini S.

Tetrahedron Lett. **43,** 5913 (2002).

13 Biginelli P.

Gazz.Chim.Ital. **23,** 360 (1893).

14 Folkers K.; Harwood H. J.; Johnson T. B.

J. Am. Chem. Soc. **54,** 3751 (1932).

15 Ehsan A.; Karimullah.

Pak. J. Sci. Ind. Res. **10,** 83 (1967).

16 Rutter H. A.; Gustafson L. O.

J. Franklin Inst. **258,** 413 (1954).

17 Mc Kinstry D.; Reading E. H.
J. Franklin Inst. **237,** 203 (1944).

18 Dubur D.; Ya.; Khanina E. L.
Khim. Geterotsikal. Soedin. 220 (1976).

19 Kastron V. V.; Vitolin R. A.; Khanina E. L.; Dubur G.; YA.; Kimenis A. A.
Khim.-Farm. Zh. **21,** 948 (1987).

20 Jani M. K.; Undavia N. K.; Trivadi P.
J. Ind. Chem. Soc. **67,** 847 (1990).

21 George T.; Tahilramani R.; Metha D. V.
Synthesis. 405 (1975).

22 Konyukov V. N.; Sakovich G. S.; krupnova L. V.; Pushkareva Z. V.
*Zh.Org.Khim.***1,** 1487 (1965).

23 Kryukov V. N.; Lebedeva N. Yu.; Kostrova S. M.
Zh. Obshch. Khim. **60,**1066 (1990).

24 Ertan M.; Balkan A.; Sarac S.; Uma S.; Ruebseman K.; Renaud J. F.
Arzneim.-Forsch. **41,** 725 (1991).

25 Ertan M.; Balkan A.; Sarac S.; Uma S.; Renaud J. F. Rolland Y.;
Arch. Pharm. **324,**135 (1991).

26 Jain S. M.; Khajuria R. K.; Dhar K. L.; Singh S.; Singh G. B.
Ind. J. Chem. **30B,**805 (1991).

27 Sadanandam Y. S.; Shetty M. M.; Diwan P. V.
Eur. J. Med. Chem. **27,** 87 (1992).

28 Zigeuner G.; Knopp C.; Blaschke H.
Monatsh Chem. **107,**587 (1976).

29 Zigeuner G.; Hamberger H.; Blaschke H.; Sterk H.
Monatsh Chem. **97,** 1408 (1966).

30 Kato T.; Chiba T.; Sasaki M.
Yakugaku Zasshi. **101,** 182 (1981).

31 Buzueva A. M.
Khim.Geterotsikal. Soedin. 345 (1969).

32 Hull R.; Swain G.
Brit. Patent Appl. 868030 (1958).
Chem. Abstr. **62,** 1463c (1962).

33 Hull R.;
Brit. Patent Appl. 984365 (1965). *Chem. Abstr.* **62,** 13159f (1965).

34 Chiba T.; Sato H.; Kato T.
Heterocycles. **22,** 493 (1984).

35 Hirao I.; Kato Y.; Hujimoto T.
Nippon Kagaku Zasshi. **85,** 52 (1964).

36 Kappo C. O.; Uray G.; Roschger P.; Lindner W.; Kratky C.; Keller W.
Tetrahedron. **48,** 5473 (1992).

37 Khanina E. L.; Siliniece G.; Ozols J.; Dubur G.; Kimenis A.
Khim.-Farm. Zh. **12,** 72 (1978).

38 Kadis V.; Stradins J.; Khanina E. L.; Dubur G.; Muceniece D.
Khim. Geterotsikl. Soedin. 117 (1985).

39 Dubur G.; Khanina E. L.; Vitolins R.
USSR Patent. 422735 (1974).
Chem. Abstr. **81,** 91549x (1974).

40 Khanina E. L.; Andaburskaya M. B.; Dubur G.; Zolotoyabko R. M.
Latv. PSRZinat. Akad. Vestis. Kim. Ser. 197 (1978).
Chem Abstr. **89,** 43319r (1978).

41 Khanina E. L.; Dubur G.;
Khim. Geterotsikl. Soedin. 535 (1982).

42 Khanina E. L.; Mucenice D.; Kadysh V. P.; Dubur G.
Khim. Geterotsikl. Soedin. 1223 (1986).

43 Sweet F. Fissekis J. D.;
J. Am. Chem. Soc. **95,** 8741 (1973).

44 Khanina E. L.; Zolotoyabko R. M.; Muceniece D; Dubur G.
Khim. Geterotsikl. Soedin. 1076 (1989).

45 Folkers K.; Johnson T. B.
J. Am. Chem. Soc. **55,** 2886 (1933).

46 Kappo C. O.; Roschger P.
J. Heterocycl. Chem. **26,** 55 (1989).

47 Robinett L. D.; Yager K. M.; Phelan J. C.
American Chemical Society. Washington, DC, 1996; ORGN 122.

48 Shutalev A. D.; Kishko E. A.; Sivova N. V.; Kuznetsov A. Yu.
Molecules. **3,** 100 (1998).

49 Hentrich W.; Schepss W. (I. G. Ferbenind.) D.R.P. 547057 (1930).
Fortschr. Teerfrabenfabr. Verw. Industriezweige. **25,** 2590 (1932).

50 Mc Kinstry D. W.; Reading E. H.
J. Franklin Inst. **237,** 422 (1944).

51 Kato T.
Japn. Kokai. Tokkyo Koho JP. 59190974 (1984). *Chem. Abstr.* **102,** 132067 (1985).

52 Bozing D.; Benko P.; Petocz L.; Szecsey M.; Toempe P.; Gigler G.; Gacsalyi I.
Eur. Pat. Appl. EP. 409233 (1991). *Chem. Abstr.* **114,** 247302z (1991).

53 Godfraind T.; Miller R.; Wibi M.
Pharmacol. Rev. **38,** 321 (1986).

54 Kastron V. V.; Vitolina R.; Khanina E. L.; Dubурs G.; Kimenis A.; Kondratenko N. V.; Popov V. I.
US Patent 4738965 (1988). *Chem. Abstr.* **110,** 18547h (1989).

55 Vitolina R.; Kimenis A.
khim.-Farm. Zh. **23,** 285 (1989).

56 Atwal K. S.; Rovnyakg. C.; Schwartz J.; Moreland S.; Hedberg A.; Gougoutas J. Z.; Malley M. F.;Floyd D. M.
J.Med. Chem. **33,** 1510-1515 (1990).

57 Kurono M.; Hayashi M.; Miura K.; Isogowa Y.; Sawai K.
Jpn. Kokai Tokkyo Koho JP. 62267272 (1987). *Chem. Abstr.* **109,** 37832t (1988).

58 Takatani T.; Takasugi H.; kuno A.; Inoue Z.
Jpn. Kokai Tokkyo Koho JP. 62252775 (1987). *Chem. Abstr.* **109,** 6538x (1988).

59 Mishina T.; Tsuda N.; Inui A.; Miura Y.
Jpn. Kokai Tokkyo Koho JP. 62169793 (1987). *Chem. Abstr.* **108,** 56120e (1988).

60 Atwal K. S.; Moreland S.
Bioorgan. Med. Chem. Lett. **1,** 291 (1991).

61 Baldwin J. J.; Pitzenberger S. M.; Mc Clure D. E.
US Patent 4675321 (1987). *Chem. Abstr.* **107,** 242619d (1987).

62 AtwalK. S.; RovnyakG. C.; KimballD. S.; David M. F.; Suzanne M.; Brian N. S.; Jack Z. G.; Joseph S.; Kaye M. S.; Mary F. M.
J. Med. Chem. **33,** 2629 (1990).

63 Cho S.; Miyazaki Y.
Jpn. Kokai Tokkyo Koho JP. 6287574 (1987). *Chem. Abstr.* **107,** 134321s (1987).

64 Cho H.; Ueda M.; ShimaK.; Mizuno A.; Hayashimatsu M.; Ohanaka Y.; Takeuchi Y.; Hamaguchi M.; Aisaka K.; Hidaka T.; Kawai M.; Takeda M.; Ishihara T.; Funahashi K. *J. Med. Chem* **32,** 2399 (1989).

65 Karnail S. Atwal ;George C. Rovnyak; Brian C. O'Reilly; Joseph Schwartz. *J.Org. Chem.* **54,** 5898 (**1989**).

66 Hull R.; Swain G. *British Patent.* 868030 (1961).

67 McKin-stry D.; Reading E. H. *J. Franklin Inst.* **237,** 203 (1944).

68 Hurst E. W.; Hull R. *J. Med. Pharm. Chem.* **3,** 215 (1961).

69 Khania E. L.; Sillinietse G.; Dabur, G. Ya.;Kimenis A. A. *Khim. Pharm. Zh.* **78,** 1321 (1978).

70 Mayer T. U.; Kapoor T. M.; Haggarty S. J.; King R. W.; Schreiber S. L.; Mitchison T. *J. Science.* **286,** 971 (1999).

71 Haggarty S. J.; Mayer T. U.; Miyamoto D. T.; Fathi R.; King R. W.; Mitchison T. J.; *Chem. Biol.* **7,** 275 (2000).

72 Lebl M. *J. Comb. Chem.* **1,** 3-24 (1999).

73 Thompson L. A.; Ellman J. A. *Chem. Rev.* **96,** 555-600 (1996).

74 Fox S.; Farr-Jones S.; Yund M. A. *J. Biomol. Screening.* **4,** 183-186 (1999).

75 Kappe C. O. *Eur. J. Med. Chem.* **35,** 1043-1052 (2000).

76 Kappe C. O. *Acc. Chem. Res.* **33,** 879-888 (2000).

77 Dondoni A.; Massi A.; Sabbatini S. *Tetrahedron Lett.* **43,** 5913-5916 (2000).

78 Kappe C. O.; Shishkin O. V.; Uray G.; Verdino P. *Tetrahedron.* **56,** 1859-862(2000).

79 Khodjakov A.; Copenagle L.; Gordon M. B.; Compton D. A.; Kapoor T. M. *J. Cell. Biol.* **160,** 671-683(2000).

80 Hauf S.; Cole R. W.; LaTerra S.; Zimmer C.; Schnapp G.; Walter R.; Heckel A.; van Meel J.; Rieder C. L.
J. Cell Biol. **161,** 281-294 (2003).

81 DeBonis S.; Simorre J. P.; Crevel I.; Lebeau L.; Skoufias D. A.; Blangy A.; Ebel C.; Gans P.; Cross R.; Hackney D. D.; Wade R. H.; Kozielski F.
Biochemistry. **42,** 338-349 (2003).

82 Maliga Z.; Kapoor T. M.; Mitchinson T. J.
J.Chem. Biol. **9,** 989-996 (2002).

83 Ochi T.
Mutat. Res. **499,** 73-84 (2002).

84 Kapoor T. M.; Mitchinson T. J.
J. Cell. Biol. **154,** 1125-1133 (2001).

85 Kapoor T. M.; Mayer T. U.; Coughlin M. L.; Mitchinson T. J.
J. Cell. Biol. **4,** 975-988 (2002).

86 Lecnik O.; Schimd M. G.; Kappe C. O.; Gubitz G.
Electrophoresis. **22,** 3198-3202 (2001).

87 Dondoni A.; Massi A.; Sabbatini S.; Bertolasi V.
J. Org. Chem. **67,** 6979-6994 (2002).

88 Crews C. M.; Mohan R.
Curr. Opin. Chem. Biol. **67,** 47-53 (2000).

89 George C. Rovnyak, Karnail S. Atwal, Anders Hedberg S., David Kimball, Suzanne Moreland, Jack Z.Gougoutas, Brian C. O'Reilly, Joseph Schwartz, Mary F. Malleys.
J.Med. Chem. **35,** 3254-3263 (1992.)

90 Edward J. Wojcik, Nadine A. Dalrymple, Shannon R. Alford, Richard A. Walker.
Biochemistry (2004)

91 Sally-Ann Poulsen, Ronald J. Quinn.
J. Med. Chem. **39,** 4156-4161 (1996).

92 Davies L. P.; Brown D. J.; Chow S. C.; Johnston G. A. R.
Neurosci. Lett. **41,** 189-193 (1983).

93 Davies L. P.; Chow S. C.; Skerritt J. H.; Brown D. J.; Johnston G. A. R.
Life Sci. **34,** 2117-2128 (1984).

94 Salvatore DeBonis, Jean-Pierre Simorre, Isabelle Crevel, Luc Lebeau, Dimitrios A. Skoufias, Anne Blangy, Christine Ebel, Pierre Gans, Robert Cross, David D. Hackney,
Biochemistry. **42,** 338-349 (2003).

95 Alessandro Dondoni, Alessandro Massi, Simona Sabbatini, Valerio Bertolasi.
J. Org. Chem. **67,** 6979-6994 (2002).

96 Antonello Mai, Marino Artico, Gianluca Sbardella, Silvana Quartarone, Silvio Massa, Anna G. Loi, Antonella De Montis, Franca Scintu, Monica Putzolu, PaoloLa Colla.
J. Med. Chem. **40,** 1447-1454 (1997).

97 Antonello Mai, Marino Artico, Gianluca Sbardella, Silvio Massa, Ettore Novellino, Giovanni Greco, Anna Giulia Loi, Enzo Tramontano, Maria Elena Marongiu, Paolo LaColla
J. Med. Chem. **42,** 619-627 (1999).

98 Tanaka H.; Baba M.; Hayakawa H.; Sakamaki T.; Miyasaka T.; Ubasawa M.; Takashima H.; Sekiya K.; Nitta I.; Shigeta S.; Walker R. T.; Balzarini J.; De Clercq. *E.*
J. Med. Chem. **34,** 349-357 (1991).

99 Baba M.; Shigeta S.; Tanaka H.; Miyasaka T.; Ubasawa M.; Umezu K.; Walker R. T.; Pauwels R.; De Clercq E.
Antiviral Res. **17,** 245-264 (1992).

100 Botta M.; Artico M.; Massa S.; Gambacorta A.; Marongiu M. E.; Pani A.; La Colla P.
Eur. J. Med. Chem. **27,** 251-257 (1992).

101 Artico M.; Massa S.; Mai A.; Marongiu M. E.; Piras G.; Tramontano E.; La Colla P.
Antiviral Chem. Chemother. **4,** 361-368 (1993).

102 Tramontano E.; Marongiu M. E.; De Montis A.; Loi A. G.; Artico M.; Massa S.; Mai A.; La Colla P.
Microbiologica. **17,** 269-279 (1994).

103 Massa S.; Mai A.; Artico M.; Sbardella G.; Tramontano E.; Loi A. G.; Scano P.; La Colla.
Antiviral Chem. Chemother. **6,** 1-8 (1995).

104 Mai A.; Artico M.; Sbardella G.; Massa S.; Loi A. G.; Tramontano E.; Scano P.; La Colla P.
J. Med. Chem. **38,** 3258-3263 (1995).

105 Sondhi S. M.; Goyal R. N.; Lahoti A. M.; Singh N.; Shukla R.; Raghubir R.
Bioorg. Med. Chem. **9,** 3185 (2005).

106 Massey A.; Xu YZ.; Karran P.
DNA Repair (Amst). **4,** 275-86 (2002).

107 Shigeta S.; Mori S.; Watanabe F.; Takahashi K.; Nagata T.; Koike N.; Wakayama T.; Saneyoshi M.
Antivir Chem Chemother. **2,** 67-82 (2002).

108 Attia A. M.; Sallam M. A.; Almehdi A. A.; Abbasi M. M.
Nucleosides Nucleotides. **10,** 2307-15 (1999).

109 Shigeta S.; Mori S.; Kira T.; Takahashi K.; Kodama E.; Konno K.; Nagata T.; Kato H.; Wakayama T,.; Koike N.; Saneyoshi M.
Antivir Chem Chemother. **4** 195-209 (1999).

110 Rahim S. G.; Trivedi N.; Bogunovic-Batchelor M. V.; Hardy G. W.; Mills G.; Selway J. W.; Snowden W.; Littler E.; Coe P. L.; Basnak I.; Whale R. F.; Walker R. T.
J Med Chem. **39(3)** 789-95 (1996).

111 Massey A.; Xu YZ.; Karran P.
Curr Biol. **11(14)** 1142-6 (2001).

112 Jeong L. S.; Kim Y. H.; Kim H. O.; Yoo S.J.; Park Y.H.; Yeon S.H.; Chun M. W.; Kim H. D.
Nucleosides Nucleotides Nucleic Acids. **20(4-7)** 665-8 (2001).

113 Palomino E.; Meltsner B. R.; Kessel D; Horwitz J. P.
J Med Chem. **33(1)** 258-63 (1990).

114 Yamamoto Y.; Yokoyama S.; Miyazawa T.; Watanabe K.; Higuchi S.
FEBS Lett. **157(1)** 95 (1983).

115 Bassleer R.; de Paermentier F.; Lepoint A.; Lhoest-Gauthier M. P.; Jamoulle J. C.; Lapiere C. L.
C. R. Acad Sci Hebd Seances Acad Sci D. **287(4)** 369-71 (1978).

116 Max H. Iltzsch, Kevin O. Tankersley.
Biochemical Pharmacology. **48(4),** 781-791 (1994).

117 Pfefferkorn E. R.
Exp Parasital **44,** 26–35 (1978).

118 Pfefferkorn.
Exp Parasital **69,** 129–139 (1989).

119 Kwong L. K.; Moore V. G.; Kaiser II.
J Biol Chem. **252(18)** 6310-5 (1997).

120 Bassleer R.; De Paermentier F.; Jamoulle J. C.; Lapiere C. L.
C. R. Acad Sci Hebd Seances Acad Sci D. **284(10)** 859-61 (1977).

121 Raymond H. Lindsay, Billie sue Hulsey ,Hassan Y. Aboul-Enein.
Biochemical Pharmacology. **24(4),** 463-468 (1975).

122 Lonberg-Holm K.; Gosser L. B.; Kauer J. C.
J Gen Virol. **27(3)** 329-42 (1975).

123 Sunil K. Mazumdar, Wolfram Saenger, Karl Heinz Scheit.
Journal of Molecular Biology. **85(2),** 213-216 (1974).

124 Bo Sörbo, Bo Lundberg.

Biochimica et Biophysica Acta (BBA) - Nucleic Acids and Protein Synthesis. **157,** 445-454 (1968).

125 E. Spector ,F. E. Shideman.
Biochemical Pharmacology. **2(3),** 182-184 (1959).

126 V. M. Parikh;
Absorption spectroscopy of organic molecules, Addition-Wesley Pub. Co. London 243, 258 (1978). A. Hand book of spectroscopic data by B. D. Mishtry; 1st ed. ABD Press Jaipur 11-36 (2000).

127 A. R. Kartizky and R. Alans Jones;
J. Chem. Soc., 2942 (1960). Introduction of Infra fed and Raman spectroscopy by Norman B. Colthup, Lowrence H. Daly and Stephan E. Wiberluy. Academic Press (1975).

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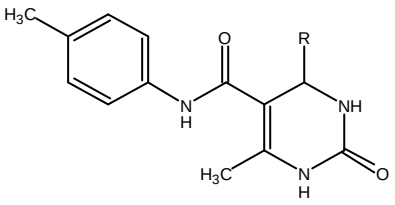
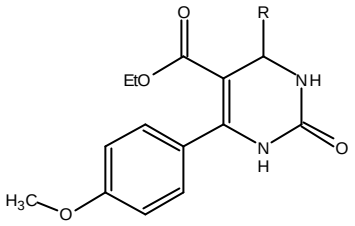
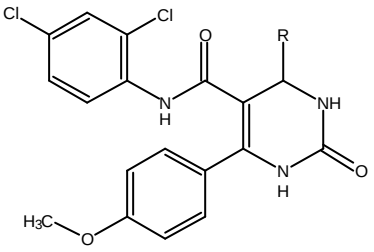


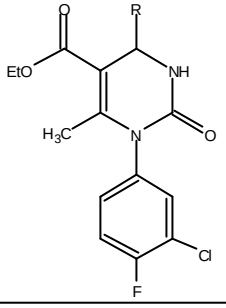
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	4-F-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2-OH-C_6H_4-
T	4-OH-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	3-C_6H_5-O-C_6H_4-
T	$C_{10}H_7$-



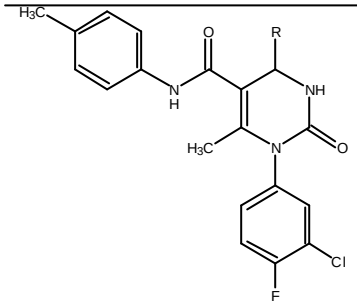
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	4-F-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-OCH_3-C_6H_4-
T	4-OH-C_6H_4-
T	2-OH,4-OCH_3-C_6H_3-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	3-C_6H_5-O-C_6H_4-
T	$C_{10}H_7$-



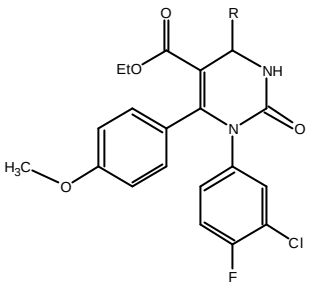
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	4-CI-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	2-OH-C_6H_4-
T	4-OH-C_6H_4-
T	4-F-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	4-$N(CH_3)_2$-C_6H_4-



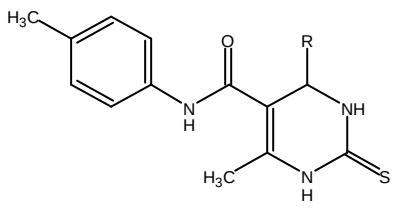
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-F-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	2-OH-C_6H_4-
T	2-OH,4-OCH_3-C_6H_3-
T	4-OH-C_6H_4-
T	4-$N(CH_3)_2$-C_6H_4-



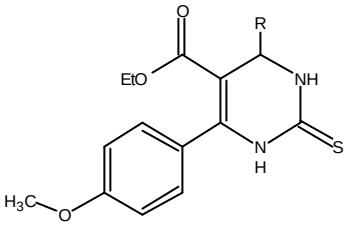
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-F-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	2-OH-C_6H_4-
T	2-OH,4-OCH_3-C_6H_3-
T	4-OH-C_6H_4-
T	4-$N(CH_3)_2$-C_6H_4-



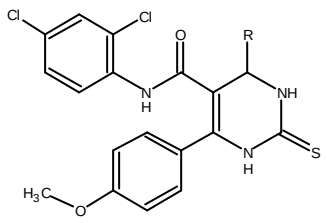
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	4-CI-C_6H_4-
T	4-F-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	4-OH-C_6H_4-
T	2-OH,4-OCH_3-C_6H_3-
T	4-$N(CH_3)_2$-C_6H_4-



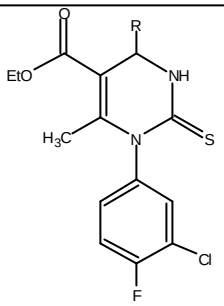
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-F-C_6H_4-
T	3-OCH_3-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2-OH-C_6H_4-
T	4-OH-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	3-C_6H_5-O-C_6H_4-



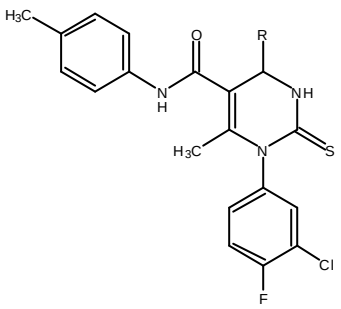
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-F-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	2-OH-C_6H_4-
T	4-OH-C_6H_4-
T	2-OH,4-OCH_3-C_6H_3-
T	4-$N(CH_3)_2$-C_6H_4-



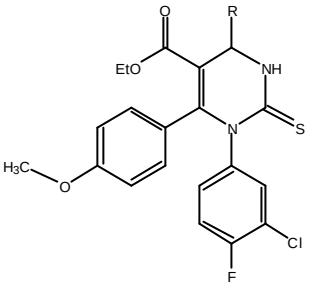
	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	4-CI-C_6H_4-
T	4-F-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	2-OH-C_6H_4-
T	2-OH,4-OCH_3-C_6H_3-
T	4-$N(CH_3)_2$-C_6H_4-



	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	4-CI-C_6H_4-
T	4-F-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2-OH-C_6H_4-
T	4-OH-C_6H_4-
T	2-OH,4-OCH_3-C_6H_3-
T	4-$N(CH_3)_2$-C_6H_4-



	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	4-CI-C_6H_4-
T	4-F-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-OCH_3-C_6H_4-
T	2-OH-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	2-OH,4-OCH_3-C_6H_3-
T	3-C_6H_5-O-C_6H_4-



	R
T	C_6H_5-
T	2-Cl-C_6H_4-
T	3-CI-C_6H_4-
T	4-CI-C_6H_4-
T	4-F-C_6H_4-
T	2-NO_2-C_6H_4-
T	3-NO_2-C_6H_4-
T	4-OCH_3-C_6H_4-
T	4-OH-C_6H_4-
T	2,5-$(OCH_3)_2$-C_6H_3-
T	2-OH,4-OCH_3-C_6H_3-
T	4-$N(CH_3)_2$-C_6H_4-